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FEBRUARY

SHOW A LEG

"Came the dawn". Of all the words—and they must have run into hundreds of thousands—put together by the gifted creatures who wrote the sub-titles in the days of silent films, these three only are remembered. The dawn, when it did come, was generally welcome. The solitary horseman, silhouetted against it, meant that help was on the way; the stockade, a-bristle with the arrows of the Redskins, would be relieved, the cruel thongs which bound the heroine to the permanent way would be severed in the nick of time.

Upon the British in February the impact of dawn is less auspicious. Some people are better at getting up than others, but only a few invite our hostile incredulity by pretending that they like doing it. The daily round, the common task, viewed with half-open eyes from the sanctuary of our pillow, arouse in us a vehement repugnance. Why on earth, we wonder, did *homo sapiens* never take up hibernation?

Yet, somehow, day after day, we survive, by a supreme effort of the will, this test of character, and once we are out of bed, routine, like a conveyor-belt, bears us steadily forward out of oblivion and into the world. The day that dawn has ushered in is unlikely, for most of us, to include any hairbreadth escapes or last-minute rescues; but it will hardly prove as lacklustre as it appeared from our pillow.

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BRITISH MEDICAL JOURNAL

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THE BASIS OF SENSATION*

SOME RECENT STUDIES OF OLFACTION

BY

E. D. ADRIAN, O.M., M.D., D.Sc., F.R.C.P., P.R.S.

Master of Trinity College, Cambridge

It is probably inevitable that there should be a period when successive Banting lecturers will find themselves with little to say about their proper theme. We commemorate a man whose work was directly responsible for the prolongation of many million lives, whose biography should be far more interesting than that of most successful scientists. But those best qualified to give a picture of his unusual talents have already spoken, and he did not live so long ago that the lecturer can deal with the historical setting of his career. Successive Harveian Lectures add to our knowledge of Harvey's discoveries by describing the theories and politics of the Jacobean age: it is so far away and the thought of that period is so different from ours that the more we hear about it the better we shall understand Harvey. But the period of the first world war is too close to many of us to be treated objectively. A century hence historians may have plausible theories to show why we thought and acted as we did, and may try to explain why the sustained emotional pressure of the first war seemed different in quality from that of the second; but these lectures will be much more convincing when there is no one left alive to say that we did not feel like that.

Impressions from a Wartime Meeting

I am, in fact, too much a contemporary of Banting to pass historical judgment, and I had too little contact with him for personal reminiscence. Indeed, I met him only once—at the beginning of the second world war, when he was on a mission in England. Naturally it was difficult not to colour one's impression of him to match the almost legendary background of the insulin period, but even if one had known nothing about it I think one would have set him down as a man capable of great achievement. He was gentle and friendly, but one could feel his energy and determination. I had the impression that he would grasp at the essentials and be impatient of the details, and that he would face the simple issues which never occur to subtle but more conventional minds; and, of course, like all of us, he wanted very badly to be doing something. I think my strongest impression is of this impelling desire for action: since he had once scored so notably by taking the bull by the horns, he might have been even more impatient than he was. But he certainly gave me the impression of someone who had it in him to take the bull by the horns again and would put through what he wanted to do by convincing everyone not so much that it was the best and the only thing to do, but that he would not rest till he had done it.

Soon after that he was killed, but, whatever he might have done, it is difficult to believe that the outcome could have satisfied his vision of what science might accomplish. His laurels came early, and he was not the kind of man to think he had done all that he ought to do. That was how he seemed at a brief meeting in the last war, and I have mentioned that impression because it is still curiously vivid. But wartime memories are notoriously coloured by the mood we were in; at that time the prevailing mood of biologists and medical scientists led them to believe that their science could have great practical uses in war if people in high office could only be persuaded to grant facilities and if the scientist could make up his mind what he wanted them for. The medical history of the war shows that they were not far wrong. But these were prodromal symptoms; after the temperature rose in the summer of 1940 we should probably have shown a different complexion. In this place where Banting lived and worked you know far better what sort of man he was, and it is enough for me to set down my feeling of the unusual kind of ability and courage which made him still a leader, not at all weighed down by the thought that no one could score again as he had done twenty years before.

Banting and Best's work has saved innumerable lives, but it has another reason to make it memorable—the fact that it was conceived by a young medical practitioner, able and ambitious, but with little training in research. It stands, therefore, as a constant beacon to young people who enter on the study of physiology or medicine and are not content to think as they are told. It should encourage them to believe that the first sight of the wood may give the clue that cannot be seen by all the experienced professors who are lost among the trees. Most of us are more or less lost and would be grateful for fresh light, though the older we get the more grudgingly we might accept it. At all events, most of us could point to chapters in the textbooks which seem to need the fresh outlook of a mind not weighed down by too much knowledge of details. Advertising our difficulties may not be the best way of getting out of the wood, for if our hearers paid much attention to what we told them we should

*Banting Memorial Lecture delivered in Toronto on September 16, 1953.

drag them into the forest to share our obscurity. But it is better to speak of the mess we are in ourselves than to enlarge on that of our colleagues; and so the best tribute I can pay to Banting's memory must be to tell you how much we want new light in the field I know best, that of the physiology of sensation.

A Fundamental Difficulty

There is, first of all, a fundamental difficulty which does not seem to me to be soluble at all by experimental science—the difficulty of connecting physical and mental events, of bringing sensations and thoughts into the framework that we use so effectively for describing our external world. I cannot myself see how further knowledge of brain physiology will help us to reconcile mind and matter, but I am prepared to believe that a hundred years hence it will be difficult to understand why we ever puzzled about it. Even now there are many scientists and many philosophers who themselves find no difficulties and think they arise from faulty premises and outworn habits of thought. They may well be right. I should have more courage in thinking them wrong if I could forget the curious chapter in the history of biology when the scientific world was divided between the Ovists, who held that the embryo was a development of the ovum alone, and the Animalculists, who held that it was essentially a development of the spermatozoon. The notion that it might come from both together seemed too absurd to be considered—until something happened to break the spell and the joint origin became a reasonable idea.

No doubt the Renaissance produced many examples of the same sort, difficulties which vanished when ideas which had seemed inherent and unchangeable were found to be out of date. And so I am ready to believe that future generations will not find it as difficult as I do to include my mind in the scientific picture of the world. I am content to think that it is a puzzle for me, but that it may be no puzzle at all to someone without my particular preoccupations.

Cellular Mechanism of the Nervous System

If we discuss sensation we can scarcely leave the mind out of it, but I want to do so in what follows, for it will be mainly concerned with the cellular mechanism of the nervous system. I want to discuss the general organization of the nervous system which makes us react differently to different external events. We have a large number of receptor cells sensitive to different material changes, and we have a large number of motor neurones coupled to the muscles which produce our reactions. The environment and our reactions to it are changing all the time, and much of what we do cannot well be related to any one sensory stimulus, but it is a convenient simplification to think of a particular pattern of receptor stimulation as the cause of a particular pattern of response, and I make no apology for doing so. Admit, then, that the stimulation of certain receptors will produce a particular sequence of movement and the stimulation of others will produce a different sequence. What sort of organization is there to account for all the differential reactions which our nervous system will produce?

Obviously a great deal depends on the course of the pathways from the receptors to the motor nerve cells. We turn right or left when the stimulus is one-sided, because the signals enter the central nervous system from that side and are not evenly distributed; and we react differently to a sound or a light because the signals come by the auditory and the optic nerves and follow a different route. In less elaborately organized animals—sea anemones, for instance—each group of receptors may serve a particular group of muscle fibres; the connexions are fixed and there is no central integration. But in the vertebrates there is a great deal of integration, and that means that the connexions and the route travelled by the signals can be varied considerably. The responses are different movements, and each involves a particular spatial and temporal distribution of activity in the motor nerve cells—a particular changing pattern of excitations and inhibitions. In the same way the signals from the receptors have particular spatial and temporal distribution for each event. The afferent and the efferent pattern are partly related by anatomical connexions, but there is an intermediate region where the connexions are sometimes open and sometimes closed and where a great variety of transmission is possible.

Sensory Excitation

The gross distribution of the sensory excitation is obviously of the first importance. We can recognize and react appropriately to a spoken word because it produces a particular sequence of excitation patterns in the cochlea, and we can recognize a face because the retinal excitation has the right shape. But the receptors of the eye show us colours as well as shapes, and the receptors of the skin give sensations of hot and cold and of various sorts of pain as well as of contact. We are aware of (or, if the mind is to be kept out of it, we react to) particular qualities of the stimulus as well as to its location and its intensity. Differences in the colour of adjacent patches in the visual field may perhaps be signalled by differences in the temporal evolution of the signals from them. This would avoid the need to credit the retina with special nerve fibres for colour from each point, but we know that the skin does use a different set of fibres to signal contacts, temperature, and pain, fibres of different diameter which lead to different pathways in the spinal cord. So we must be prepared to find that a sensory surface uses a variety of fibres to signal differences in the quality of the stimulus and that the result depends both on the general distribution of the excitation and on the particular varieties of nerve fibre which convey it.

How do these different sorts of fibre produce different effects in the central nervous system, different kinds of sensation, and a different reaction of the body? Though the fibres may be intimately mixed in the nerve trunks, there is often an anatomical sorting out when they enter the central nervous system; for instance, the fibres from the skin which signal touch extend up to the brain stem, whereas the non-medullated C fibres end in the cord. Even where there is no detectable sorting out it remains an obvious possibility that fibres from different kinds of receptor may have different kinds of dendritic connexion. But we are still faced with the need for a process which balances one excitation against another, and I believe we may be mistaken in thinking of the central nervous system as though it were made up of neurones which differ only in their structural features. I think we ought to consider the possibility of some variation in their chemistry as well.

So I am going to discuss the suggestion that the neurones from different varieties of receptor may liberate somewhat different material when an impulse reaches their dendritic endings and that the precise composition of the molecular output decides which of the succeeding neurones will be stimulated. It is true that this merely substitutes differences in humoral excitants for differences in dendritic structure, and there is more evidence for the latter, but I make the suggestion because I have been forced to realize how nervous elements which look much the same may differ greatly in their chemical sensitivity.

Olfactory Receptors

I am thinking, of course, of the olfactory receptors. The nose can distinguish an immense variety of molecules brought to it in the air drawn in at each inspiration. When we smell something we are aware of the intensity of the

smell, and we can usually tell where it comes from, but our chief awareness is of pure quality without any spatial or temporal attributes. Now the olfactory receptors are nerve cells furnished with hairs, which project into the mucous layer on the olfactory surface, and at the opposite pole with a non-medullated axon, which runs through the cribriform plate to end in the olfactory bulb. The number of these cells runs into millions even in a relatively small olfactory organ like that of man, and they are so closely packed that the position of the bulge formed by the nucleus varies from cell to cell. In some the nucleus is nearer the hairs and in others nearer the axon, but this is the only histological difference visible in a stained preparation. Two kinds of olfactory hair have been described in fresh preparations from the frog, and it is possible that they are present in the mammal too, but there is no indication of any sharp division into two or more kinds of cell. In fact, the organ seems to be composed of a large surface packed with receptors which differ from one another only in the position of the nucleus in the cell and the position of the cell in the olfactory surface.

It is not possible to record the signals which pass to the olfactory bulb in the non-medullated axons, but we can record axon spikes in the neurones to which they lead. These are the mitral cells: large nerve cells with medullated axons which can be reached by a wire electrode thrust into the olfactory bulb. Since there are only 70,000 of them in the rabbit's bulb for many million receptors, the axon discharge must be a condensed version of the receptor signals, and a great deal of interaction may have taken place in the synaptic regions. But the receptors in touch with one mitral cell seem to be confined more or less to one part of the olfactory epithelium, though the extent of the receptive field is unknown.

Not only are the mitral-cell signals at one remove from the receptor signals, but they can be recorded profitably only in highly abnormal conditions, under anaesthesia deep enough to suppress all the spontaneous activity in the bulb. But if in such conditions we find that different smells give distinctive discharges they would scarcely fail to do so in the normal animal.

In the early stages, before I had learnt how to record from single units, I could get little satisfactory evidence of differential sensitivity in the receptors leading to any one point in the bulb. Smells strong enough to produce a mitral discharge would usually cause one in many units; sometimes the axon spikes seemed larger or smaller according to the nature of the stimulus, but that was all. On the other hand, there was no doubt that the different regions of the olfactory organ were not equally sensitive or equally accessible to all the molecules which could stimulate some part of it. Amyl acetate, ethyl acetate, and ether would always evoke a discharge in the anterior part of the bulb—corresponding to the anterior part of the olfactory surface—and the less volatile oils would rarely stimulate there, though they would give a large discharge at the back of the bulb. I still think that this large-scale difference in the distribution of the excitation is probably an important factor in the discrimination of smells, for in many animals the olfactory surface is so large and is folded into such complex channels that molecules of different properties carried in by the air stream would be unlikely to be deposited in an identical pattern. Another distinguishing feature may be the undoubted difference in the temporal evolution of the excitation with different substances. Volatility and solubility in water both favour a rapid rise and decline of the discharge, with little persistence between one inspiration and another. Thus the spatial and temporal pattern of the excitation will vary with the molecules which enter the nose, in much the same way as the pattern varies for the eye with the object in view and for the ear with the sound.

But these differences in timing and distribution cannot be shown to give more than a rough sorting out into a few categories, possibly dependent on the behaviour of the material in water and in lipoids. Some further discriminating mechanism is needed to account for the great variety of smell which can be recognized even by the human nose, and it is supplied by the selective sensitivity of the individual receptors.

Selective Sensitivity

This was not evident until a method was devised for exposing the rabbit's nose to a concentration of the stimulating molecules which could be increased gradually from zero, the relative strength being signalled at each moment on the record of the impulse discharges. The method is simply to send two streams of air into the facepiece which covers the snout. Both are purified by filtration through charcoal (a necessary precaution to make them inodorous), and one is passed through a small bottle containing the substance to be tested, usually in liquid form. The rate of flow of this stream can be gradually increased by opening a screw valve, and the extent of the opening is signalled on the recording film.

With this arrangement and with a suitable position of the electrode and a good cranial circulation it is nearly always possible to show that different substances in threshold concentration will employ different mitral cells for signalling the stimulus. Usually a particular substance can be found that will evoke a discharge which is confined to a single unit near enough to the electrode to give large axon spikes. Another substance may give a threshold discharge confined to another single unit, though there will often be several units in action, and none of them close enough to the electrode to give distinctive axon spikes.

A discharge confined to one mitral unit is presumably due to an excitation confined to the particular group of receptors which lead to it, and since adjacent mitral units react to different substances it follows that adjacent groups of receptors have some degree of selective sensitivity. The degree of specificity varies greatly from one unit to another. The electrode may be close to a mitral cell which is in such unstable equilibrium that a very slight lightening of the anaesthesia will make it discharge spontaneously. Such a cell will usually start a discharge when the nose is tested with a wide variety of smells, and it may be impossible to pick out one which seems to have any specific relation to that cell alone. And the specific relation is a matter of degree; when one substance gives a threshold discharge confined to a single unit, related substances will usually stimulate that unit in low concentration, though they will stimulate other units as well. For instance, if benzene vapour gives a single series of large axon spikes, toluene and xylene will evoke similar spikes, though even at the threshold they will be mixed with smaller spikes from other units.

Many substances have been used in searching for these specific effects, but no attempt has been made to cover the whole range of odours. Yet enough experiments have been made to show that the substances tested fall into distinct groups, each tending to pick out particular mitral units, and that within each group one substance usually shows the greatest specificity—that is, one substance is most often found to give a discharge limited to a single one of the units within range of the electrode. Such substances are acetone in a group which includes esters like amyl acetate and ethyl acetate, benzene in the group of aromatic hydrocarbons, octane in the group of paraffin hydrocarbons, heavy oils, etc. Dipentene, cedar-wood oil, and eucalyptus belong to the large group of terpenes and related compounds, and all three have often given single unit discharges. Probably there are many other groups—for example, mercaptans. At least ten different substances have been found to pick out a single unit, but sometimes the same unit is picked out by several substances from different groups—for example, dipentene and acetone, benzaldehyde and amyl acetate, etc. In fact, the evidence suggests that particular types of molecular configuration have an affinity for particular varieties of receptor, but that the physical properties of the substance are also important.

In view of the regional differences in sensitivity found in the earlier experiments one would expect that the units responding, for example, to acetone would be found more often in the front part of the bulb and those responding to heavy oil at the back. There is undoubtedly a segregation of this kind, although, in the middle region, unit discharges have been obtained with substances from all the groups. It is true that most of these units can be made to discharge to a wide range of stimuli if the concentration is raised, but there will always be outlying parts of the olfactory organ where it has the threshold value needed to bring out the differential effects.

Assessment of the Different Factors

A great deal remains to be done before we can assess the different factors concerned in olfactory discrimination, but the important point is that neighbouring groups of olfactory receptors have marked differences in their sensitivity to different smells. I have no doubt, therefore, that olfactory discrimination is not due solely to the complex structure of the organ—that is, to the deposition of the material in different patterns on its surface owing to differences in the rate of air flow, size of molecules, etc.

In fact the olfactory epithelium proves to be a large collection of nerve cells which look alike, apart from the position of the nucleus, but differ so much in their properties that some will be excited by a trace of acetone vapour and others by a trace of benzene. This, of course, is no more than would be expected by anyone who contemplates the remarkable discriminative power of the nose. But it is an important point to have established, and I do not regret the time I have spent in trying to develop a different hypothesis.

It may be that the point is important only in connexion with the working of the olfactory organ; the receptors there may be the only cells which have developed such a high degree of chemical discrimination. But nerve cells in other places may show traces of the same discriminative power. Let us suppose, then, that there are sheets of such cells in the central nervous system with dendrites ending freely amongst the dendrites of afferent neurones, so that material liberated from these might come into contact with the dendrites from more than one cell. It cannot be expected that the terminations of the afferent neurones would liberate molecules as different as acetone and benzene, but if some neurones liberate acetylcholine and some noradrenaline it is not impossible that the molecules liberated by the fibre from a temperature receptor might differ considerably from those liberated by a pain fibre. The ultimate destination of the different signals reaching the dendritic network would then be determinated by the different chemical sensitivities of the neurones whose dendrites are stimulated.

It is perhaps worth pointing out that the excitation of an olfactory receptor is a rapid process which ceases usually at the end of inspiration when the delivery of vapour is suspended, that the number of molecules needed to excite must be very small, and that they must be removed or neutralized rapidly. The same could be said of the excitation of a nerve cell by a humoral transmitter. I am bound to admit the difficulty of believing that all the different groups of molecules which stimulate the olfactory receptors are dealt with by different specific enzymes, as cholinesterase deals with acetylcholine, but they are certainly inactivated rapidly and completely.

Speculations which cannot be put to experimental test are seldom worth elaborating, and I cannot pretend that we should be in a much better position if this speculation turned out to be correct. A selective transmission determined by the nature of the material set free in the dendritic network might allow more variation than one determined by the detailed connexion of dendrites, but that is all that can be claimed for it.

Yet I think the olfactory organ may have something to teach us about the organization of the nervous system. Since its nerve cells are found to have such selective properties we must be ready to look for similar properties in nerve cells elsewhere.

Conclusion

That, I am afraid, is a poor conclusion to a lecture which commemorates a man whose researches were of such immediate practical benefit to so many people. I wish I had something better to offer than these incomplete results on a sense organ which has never roused much interest. I can still recall the intense interest which the work of Banting and Best aroused in all of us, in physiologists as well as in every doctor. But such triumphant victories come very rarely, and they are separated by the slow, plodding attack on a wide front. I have described a minor incident in that attack with a speculation attached to it; but I have done so because most of our research is like that, and because it is with such inconclusive results that you must contrast the spectacular advance which came with the finding of insulin.

PROTECTION AFFORDED BY SICKLE-CELL TRAIT AGAINST SUBTERTIAN MALARIAL INFECTION

BY

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The aetiology of sickle-cell anaemia presents an outstanding problem common to both genetics and medicine. It is now universally accepted that the sickle-cell anomaly is caused by a single mutant gene which is responsible for the production of a type of haemoglobin differing in several important respects from normal adult haemoglobin (Pauling *et al.*, 1949; Perutz and Mitchison, 1950). Carriers of the sickle-cell trait who are heterozygous for the sickle-cell gene have a mixture of this relatively insoluble haemoglobin and normal haemoglobin; hence their erythrocytes do not sickle *in vivo*, whereas some at least of the homozygotes, who have a much greater proportion of sickle-cell haemoglobin, have sickle cells in the circulating blood, with inevitable haemolysis and a severe, often fatal, haemolytic anaemia. There is also a much smaller group of sickle-cell anaemia patients who are heterozygous for the sickle-cell gene as well as for some other hereditary abnormality of haemoglobin synthesis (Neel, 1952).

It is thus possible to approach the problem from the clinical or the genetical side. From the clinical point of view it is important to distinguish between carriers of the sickle-cell trait who show no other haematological abnormalities and patients with sickle-cell anaemia, who have a haemolytic disease which can reasonably be attributed to sickling of the erythrocytes. From the genetical point of view the main distinction is to be drawn between those who are homozygous and those who are heterozygous for the sickle-cell gene. In the great majority of instances two classifications coincide—that is, most individuals with the sickle-cell trait are heterozygous and most cases of sickle-cell anaemia, in Africa at least, are homozygous for the sickle-cell gene.

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The sickle-cell trait is remarkably common in some parts of the world. Among many African negro tribes 20% or more of the total population have the trait, and frequencies of 40% have been found in several African tribes (Lehmann and Raper, 1949; Allison, 1954). In parts of Greece frequencies of 17% have been described (Choremis *et al.*, 1953), and as many as 30% of the population in Indian aboriginal groups are affected (Lehmann and Cutbush, 1952).

Wherever the sickle-cell trait is known to occur sickle-cell anaemia will also be found. For a time it was thought by some workers that sickle-cell anaemia was rare among African negroes, but so many cases have been described during the past few years that this view is no longer tenable (Lambotte-Legrand and Lambotte-Legrand, 1951; Foy *et al.*, 1951; Edington, 1953; Vandepitte and Louis, 1953).

The main problem can be stated briefly: how can the sickle-cell gene be maintained at such a high frequency among so many peoples in spite of the constant elimination of these genes through deaths from the anaemia? Since most sickle-cell anaemia subjects are homozygotes, the failure of each one to reproduce usually means the loss of two sickle-cell genes in every generation. It can be estimated that for the lost genes to be replaced by recurrent mutation so as to leave a balanced state, assuming that the sickle-cell trait—that is, the heterozygous condition—is neutral from the point of view of natural selection, it would be necessary to have a mutation rate of the order of 10^{-1}. This is about 3,000 times greater than naturally occurring mutation rates calculated for man and, with rare exceptions, in many other animals—3.2×10^{-5} in the case of haemophilia (Haldane, 1947). A mutation rate of this order of magnitude can reasonably be excluded as an explanation of the remarkably high frequencies of the sickle-cell trait observed in Africa and elsewhere.

Possibility of Selective Advantage

Of the other explanations which can be advanced to meet the situation, one has received little attention: the possibility that individuals with the sickle-cell trait might under certain conditions have a selective advantage over those without the trait. It was stated for many years that the sickle-cell trait was in itself a cause of morbidity, but this belief seems to have been based upon unsatisfactory criteria for distinguishing the trait from sickle-cell anaemia. The current view is that the sickle-cell trait is devoid of selective value. Henderson and Thornell (1946) found that in American negro air cadets who had passed a searching physical examination the incidence of the sickle-cell trait was the same as in the general negro population of the United States. Lehmann and Milne (1949) were unable to discover any correlation between haemoglobin levels and the presence or absence of the sickle-cell trait in Uganda Africans. And Humphreys (1952) could find no evidence that the sickle-cell trait was responsible for any morbidity in Nigerian soldiers.

However, during the course of field work undertaken in Africa in 1949 I was led to question the view that the sickle-cell trait is neutral from the point of view of natural selection and to reconsider the possibility that it is associated with a selective advantage. I noted then that the incidence of the sickle-cell trait was higher in regions where malaria was prevalent than elsewhere. The figures presented by Lehmann and Raper (1949) for the frequency of the sickle-cell trait in different parts of Uganda lent some support to this view, as did the published reports from elsewhere. Thus the trait is fairly common in parts of Italy and Greece, but rare in other European countries; in Greece the trait attains its highest frequencies in areas which are conspicuously malarious (Choremis *et al.*, 1951).

Relation between Malaria and Sickle-cell Trait

Other reports appeared suggesting more directly that there might be a relationship between malaria and the sickle-cell trait. Beet (1946) had observed that in a group of 102 sicklers from the Balovale district of Northern Rhodesia only 10 (9.8%) had blood slides showing malaria parasites, whereas in a comparable group of 491 non-sicklers 75 (15.3%) had malaria parasites. The difference in incidence of malaria in the two groups is statistically highly significant ($\chi^2=19.349$ for 1 d.f.)*; hence Beet's figures imply strongly that malaria is less frequent among individuals with the sickle-cell trait than among those without the trait. The difference in malarial susceptibility between sicklers and others seemed to be most pronounced at the time of the year when malaria transmission was lowest.

Later, in the Fort Jameson district of Northern Rhodesia, Beet (1947) found that the same difference was present, although it was much less pronounced. Of 1,019 non-sicklers, 312 (30.6%) had blood slides with malaria parasites, whereas of 149 sicklers 42 (28.2%) showed malaria parasites. This difference is not statistically significant. However, among the sicklers from Fort Jameson enlarged spleens were less common than among non-sicklers. In a series of 569 individuals there were 87 with the sickle-cell trait; 24 (27.9%) of these had palpable spleens, as compared with 188 (39.0%) with splenomegaly out of 482 non-sicklers. This difference is again statistically significant ($\chi^2=4.11$ for 1 d.f.). Beet concluded that Africans with the sickle-cell trait were probably liable to recurrent attacks of thrombosis, with resultant shrinkage of the spleen.

Brain (1952a), also working in Rhodesia, confirmed Beet's observation that the spleen is palpable in a much lower proportion of sicklers than of non-sicklers; he went on to suggest that the finding might be explained by diminished susceptibility to malaria on the part of the sicklers. Moreover, Brain (1952b) compared the proportion of hospitalized cases in groups of African mine-workers with and without the sickle-cell trait. He found that the sicklers actually spent less time in hospital, on an average, than did the control group of non-sicklers. The incidence of malaria and pyrexias of unknown origin was much lower in the group with sickle cells.

It became imperative, then, to ascertain by more direct methods of investigation whether sickle cells can afford some degree of protection against malarial infection, thereby conferring a selective advantage on possessors of the sickle-cell trait in regions where malaria is hyperendemic. An opportunity to do this came during the course of a visit to East Africa in 1953.

Incidence of Malarial Parasitaemia in African Children with and without the Sickle-cell Trait

The observations of Beet and of Brain on differences in parasite rates and spleen rates are open to criticism because the populations were heterogeneous and were drawn from relatively wide areas. It was decided, therefore, to carry out similar tests on a relatively small circumscribed community, where all those under observation belong to a single tribe. Children were chosen rather than adults as subjects for the observations so as to minimize the effect of acquired immunity to malaria. The recorded incidence of parasitaemia in a group of 290 Ganda children, aged 5 months to 5 years, from the area surrounding Kampala (excluding the non-malarious township) is presented in Table I. The presence of sickling was demonstrated by chemical reduction of blood with isotonic sodium metabisulphite (Daland and Castle, 1948). Fresh reducing solutions were made up daily.

*These and other statistics in this paper are my own, using available figures.

TABLE I

	With Parasitaemia	Without Parasitaemia	Total
Sicklers	12 (27·9%)	31 (72·1%)	43
Non-sicklers ..	113 (45·7%)	134 (53·3%)	247

It is apparent that the incidence of parasitaemia is lower in the sickle-cell group than in the group without sickle cells. The difference is statistically significant ($\chi^2=5.1$ for 1 d.f.). In order to test as many families as possible only one child was taken from each family. There is no reason to suppose that these groups are not comparable, apart from the presence or absence of the sickle-cell trait.

The parasite density in the two groups also differed: of 12 sicklers with malaria, 8 (66.7%) had only slight parasitaemia (group 1 on an arbitrary rating), while 4 (33.3%) had a moderate parasitaemia (group 2). Of the 113 non-sicklers with malaria, 34% had slight parasitaemia (group 1), the parasite density in the remainder being moderate or severe (group 2 or 3).

It may be noted, incidentally, that of the four cases in the sickle-cell group with moderate parasitaemia three had *P. malariae*, even though this species is much less common than *P. falciparum* around Kampala. It seems possible from these and other observations that the protection afforded by the sickle-cell trait is more effective against *P. falciparum* than against other species of plasmodia, but much further work is necessary to decide the point.

These results suggest that African children with the sickle-cell trait have malaria less frequently or for shorter periods, and perhaps also less severely, than children without the trait. Further evidence regarding the protective action of the sickle-cell trait could be obtained only by direct observation on the course of artificially induced malarial infection in volunteers.

Progress of Malarial Infection in Adult Africans with and without the Sickle-cell Trait

Fifteen Luo with the trait and 15 Luo without the trait were accepted for this investigation. All the volunteers were adult males who had been away from a malarious environment for at least 18 months. The two groups were of a similar age and appeared to be strictly comparable apart from the presence or absence of the sickle-cell trait. Two strains of *P. falciparum* were used—one originally isolated in Malaya and one from near Mombasa, Kenya; in Table II these are marked with the subscripts 1 and 2 respectively. The infection was introduced by subinoculation with 15 ml. of blood containing a large number of trophozoites (B in the table) or by biting with heavily infected *Anopheles gambiae* (M in the table). At least 3 out of the 10 mosquitoes applied had bitten each individual, and the presence of sporozoites was confirmed by dissection of the mosquitoes.

The cases were followed for 40 days. Parasite counts for each case were made by comparison with the number of leucocytes in 200 oil-immersion fields of thick films, the absolute leucocyte counts being checked at intervals. The abbreviated results of these counts are shown in Table II. In the few cases in which parasitaemia was pronounced and the symptoms were relatively severe the progress of the disease was arrested. At the end of the period of observation in every case a prolonged course of antimalarial chemotherapy was given.

Discussion

It is apparent that the infection has become established in 14 cases without the sickle-cell trait. The parasitaemia is relatively light, however, when compared with that observed in non-immune populations—for example, the Africans described by Thomas *et al.* (1953). This is to be expected: the Luo come from a part of the country where malaria is hyperendemic, and they have acquired a considerable immunity to malarial infection in childhood. This factor makes the interpretation of the observations rather more difficult; however, it could not be avoided, since all the East African tribes who have high sickling rates come from malarious areas, and the acquired immunity should operate with equal force in the groups with and without sickle-cells. The acquired immunity was actually an advantage, since the symptoms were mild and the chances of complication very slight.

In the group with sickle cells, on the other hand, the malaria parasites have obviously had great difficulty in establishing themselves, in spite of repeated artificial infec-

TABLE II

No.	Mode of Infection and Strain	Day after Infection: 8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40
Luo With No Sickle-cells																		
1	M_2 B_1	0·03	—	0·07	2·5	5·0	2·5	5·0	1·2	0·4	0·02	0·01	—	—	0·1	0·01	0·01	ST
2	M_2 B_1	—	—	—	—	—	—	—	0·03	0·13	0·41	—	—	—	—	0·03	—	ST
3	M_2 B_1	—	—	—	—	—	—	—	0·1	0·02	0·20	5·0	2·5	1·25	1·67	0·2	5·0	2·0 S
4	M_2 B_1	—	—	—	—	0·02	0·02	0·5	0·83	0·12	0·2	1·0	1·0	0·83	0·25	0·17	—	ST
5	M_2 B_2	—	—	—	—	0·05	1·0	1·67	0·25	0·05	0·07	0·25	1·2	1·0	0·03	—	—	ST
6	B_1	0·02	5·0	10·0	10·0	1·0	0·1	0·01	ST	—	—	—	—	—	—	—	—	—
7	B_2	—	—	—	—	15·0	50·0	ST	—	—	—	—	—	—	—	—	—	—
8	B_2	—	—	0·13	5·0	1·67	0·33	—	—	ST	—	—	—	—	—	—	—	—
9	B_1	—	—	—	—	5·0	—	0·1	0·5	2·5	—	1·0	0·1	2·5	10·0	5·0	0·5	ST
10	B_2	—	—	—	—	—	—	0·05	0·05	—	—	0·67	—	0·1	0·05	5·0	5·0	ST
11	B_2	—	0·05	0·3	—	—	—	0·2	ST									
12	B_2	—	—	0·3	0·3	0·3	0·1	0·3	ST									
13	B_2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	ST	
14	B_2	2·0	1·7	2·0	60·0	5·0	0·6	ST										
15	B_2	0·05	0·3	—	0·4	0·1	0·3	ST										
Luo With Sickle-cell Trait																		
1	M_1 B_2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	ST
2	M_1 B_2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	,,
3	M_1 B_1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	,,
4	M_1 B_1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	,,
5	M_1 B_1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	,,
6	M_1 B_1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	,,
7	M_1 B_1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	5·0	0·5	,,
8	M_1 B_1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	,,
9	M_1 B_1	0·7	—	—	—	—	—	—	—	—	—	0·03	0·1	0·03	0·03	—	—	,,
10	M_1 B_1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	,,
11	B_2 M_2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	,,
12	B_2 M_2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	,,
13	B_2 M_2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	,,
14	B_2 M_2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	,,
15	B_2 M_2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	,,

Figures represent parasite counts in hundreds per mm.³ of blood. ST=Stopped by chemotherapy.

tion. Only two of the cases show parasites, and the parasite counts in these cases are comparatively low. The striking difference in the progress of malarial infection in the two groups is taken as evidence that the abnormal erythrocytes in individuals with the sickle-cell trait are less easily parasitized than are normal erythrocytes.

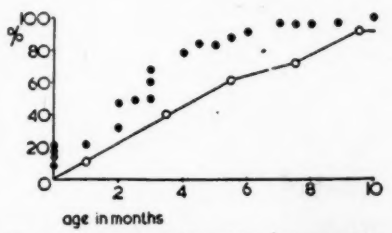
It can therefore be concluded that individuals with the sickle-cell trait will, in all probability, suffer from malaria less often and less severely than those without the trait. Hence in areas where malaria is hyperendemic children having the trait will tend to survive, while some children without the trait are eliminated before they acquire a solid immunity to malarial infection. The protection against malaria might also increase the fertility of possessors of the trait. The proportion of individuals with sickle cells in any population, then, will be the result of a balance between two factors; the severity of malaria, which will tend to increase the frequency of the gene, and the rate of elimination of the sickle-cell genes in individuals dying of sickle-cell anaemia. Or, genetically speaking, this is a balanced polymorphism where the heterozygote has an advantage over either homozygote.

The incidence of the trait in East Africa has recently been investigated in detail (Allison, 1954), and found to vary in accordance with the above hypothesis. High frequencies are observed among the tribes living in regions where malaria is hyperendemic (for example, around Lake Victoria and in the Eastern Coastal Belt), whereas low frequencies occur consistently in the malaria-free or epidemic zones (for example, the Kigezi district of Uganda; the Kenya Highlands; and the Kilimanjaro, Mount Meru, and Usumbara regions of Tanganyika). This difference is often independent of ethnic and linguistic grouping: thus, the incidence of the sickle-cell trait among Bantu-speaking tribes ranges from 0 (among the Kamba, Chagga, etc.) to 40% (among the Amba, Simbiti, etc.). The world distribution of the sickle-cell trait is also in accordance with the view presented here that malarial endemicity is a very important factor in determining the frequency of the sickle-cell trait. The genetical and anthropological implications of this view are evident.

The fact that sickle cells should be less easily parasitized by plasmodia than are normal erythrocytes is presumably attributable to their haemoglobin component, although there may be other differences, not yet observed, between the two cell-types. Sickle-cell haemoglobin is unlike normal adult haemoglobin in important physico-chemical properties, notably in the relative insolubility of the sickle-cell haemoglobin when reduced (Perutz and Mitchison, 1950). The malaria parasite is able to metabolize haemoglobin very completely in the intact red cell, the haematin pigment remaining as a by-product of haemoglobin breakdown (Fairley and Bromfield, 1934; Moulder and Evans, 1946). That plasmodia are greatly affected by relatively small differences in their environment is suggested by their remarkable species specificity. Thus the difficulty of establishing an infection in monkeys with human malaria parasites, and vice versa, is generally recognized.

How far species differences in the haemoglobins themselves, known from immunological and other studies, are responsible for the species specificity of plasmodia it is impossible to say. However, the physico-chemical differences between human adult haemoglobin and monkey haemoglobin appear to be less pronounced than the differences between either type and sickle-cell haemoglobin. It is clear that the natural resistance to malaria among individuals with the sickle-cell trait is relative, not absolute. This is perhaps attributable to differences in the expressivity of the sickle-cell gene, which may be responsible for the production of from nearly 50% to only a very small amount of sickle-cell haemoglobin (Wells and Itano, 1951; Singer and Fisher, 1953). Moreover, the sickle-cell haemoglobin may not be evenly distributed in the cell population: most observers recognize that there are cases in which only some of the red cells are sickled even after prolonged reduction. However, even a relative resistance to malaria may be enough to help those with the sickle-cell trait through the dangerous years of early childhood, during which an active immunity to the disease is developed.

The above observations focus attention upon the importance of haemoglobin to plasmodia in the erythrocytic phase. Hence it is worth considering whether erythrocytes containing other specialized or abnormal types of haemoglobin might be resistant to malaria also. Thus, human foetal haemoglobin differs from human adult haemoglobin in many properties. Red cells containing foetal haemoglobin continue to circulate in the newborn for the first three months of life, after which they are quite rapidly replaced by cells containing normal adult haemoglobin. It has long been known that the newborn has a considerable degree of resistance to malarial infection: Garnham (1949), for instance, found that in the Kavirondo district of Kenya at the end of the second month of life only 10% of babies were infected; after this age the percentage affected rises rapidly, until by the ninth month practically all children have the disease. The correspondence between the appearance of cells containing normal adult-type haemoglobin and malarial susceptibility is illustrated in the Chart. The correspondence may of course be fortuitous, but it is striking enough to merit further investigation, even though other factors, such as a milk diet deficient in *p*-aminobenzoic acid (Maegraith *et al.*, 1952; Hawking, 1953) and immunity acquired from the mother (Hackett, 1941) may play a part in the natural resistance of the newborn to malaria.



The apparent relationship between the appearance of adult-type haemoglobin (dots) and malarial infection (circles) in the newborn. Each dot represents a test on a single individual, using an alkali denaturation technique (Allison, unpublished observations); the circles represent the percentage of Luo children showing malaria parasites (Garnham, 1949).

Finally, it is possible that the explanation offered above for the maintenance of the sickle-cell trait may also apply to thalassaemia. The problems presented by the two diseases are very similar; many homozygotes, and possibly some heterozygotes, are known to die of thalassaemia, and yet the condition remains remarkably common in Italy and Greece, where as many as 10% of the individuals in certain areas are affected (Bianco *et al.*, 1952). Greek and Italian authors have commented that cases of thalassaemia usually come from districts severely afflicted wtih malaria (Choremis *et al.*, 1951). Perhaps those who are heterozygous for the thalassaemia gene suffer less from malaria than their compatriots: the fertility of the heterozygotes appears to be greater (Bianco *et al.*, 1952). Selective advantage of the heterozygote with the sickle-cell gene, and possibly the heterozygote with the thalassaemia gene also, would explain why such high gene frequencies can be attained in the case of these conditions while other genetically transmitted abnormalities of the blood cells remain uncommon, not very much above the estimated mutation rate—for example, hereditary spherocytosis (Race, 1942).

Summary

A study has been made of the relationship between the sickle-cell trait and subtertian malarial infection. It has been found that in indigenous East Africans the sickle-cell trait affords a considerable degree of protection against subtertian malaria. The incidence of parasitaemia in 43 Ganda children with the sickle-cell trait was significantly lower than in a comparable group of 247 children without the trait. An infection with *P. falciparum* was established in 14 out of 15

Africans without the sickle-cell trait, whereas in a comparable group of 15 Africans with the trait only 2 developed parasites.

It is concluded that the abnormal erythrocytes of individuals with the sickle-cell trait are less easily parasitized by *P. falciparum* than are normal erythrocytes. Hence those who are heterozygous for the sickle-cell gene will have a selective advantage in regions where malaria is hyperendemic. This fact may explain why the sickle-cell gene remains common in these areas in spite of the elimination of genes in patients dying of sickle-cell anaemia. The implications of these observations in other branches of haematology are discussed.

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REFERENCES

Allison, A. C. (1954). *Trans. roy. Soc. trop. Med. Hyg.* In press
Beet, E. A. (1946). *E. Afr. med. J.*, **23**, 75.
—— (1947). Ibid., **24**, 212.
Bianco, I., Montalenti, G., Silvestroni, E., and Siniscalo, M. (1952). *Ann. Eugen. Lond.*, **16**, 299.
Brain, P. (1952a). *British Medical Journal*, **2**, 880.
—— (1952b). *S. Afr. med. J.*, **26**, 925.
Choremis, C., Zervos, N., Constantinides, V., and Zannos, Leda (1951). *Lancet*, **1**, 1147.
—— Ikin, Elizabeth W., Lehmann, H., Mourant, A. E., and Zannos, Leda (1953). Ibid., **2**, 909.
Daland, G. A., and Castle, W. B. (1948). *J. Lab. clin. Med.*, **33**, 1082.
Edington, G. M. (1953). *British Medical Journal*, **2**, 957.
Fairley, Sir N. H., and Bromfield, R. J. (1934). *Trans. roy. Soc. trop. Med. Hyg.*, **28**, 141.
Foy, H., Kondi, A., and Brass, W. (1951). *E. Afr. med. J.*, **28**, 1.
Garnham, P. C. C. (1949). *Ann. trop. Med. Parasit.*, **43**, 47.
Hackett, L. W. (1941). *Publ. Amer. Ass. Advanc. Sci.*, **15**, 148.
Haldane, J. B. S. (1947). *Ann. Eugen., Lond.*, **13**, 262.
Hawking, F. (1953). *British Medical Journal*, **1**, 1201.
Henderson, A. B., and Thornell, H. E. (1946). *J. Lab. clin. Med.*, **31**, 769.
Humphreys, J. (1952). *J. trop. Med. Hyg.*, **55**, 166.
Lambotte-Legrand, J., and Lambotte-Legrand, C. (1951). *Institut Royal Colonial Belge, Sect. d. Sci. Nat. et Med.*, Memoires, Tome XIX, fasc. 7, p. 98.
Lehmann, H., and Cutbush, Marie (1952). *British Medical Journal*, **1**, 404.
—— and Milne, A. H. (1949). *E. Afr. med. J.*, **26**, 247.
—— and Raper, A. B. (1949). *Nature, Lond.*, **164**, 494.
Macgraith, B. G., Deegan, T., and Jones, E. S. (1952). *British Medical Journal*, **2**, 1382.
Moulder, J. W., and Evans, E. A. (1946). *J. biol. Chem.*, **164**, 145.
Neel, J. V. (1950). *Cold Spr. Harb. Symp. quant. Biol.*, **15**, 141.
—— (1952). *Blood*, **7**, 467.
Pauling, L., Itano, H. A., Singer, S. J., and Wells, I. C. (1949). *Science*, **110**, 543.
Perutz, M. F., and Mitchison, J. M. (1950). *Nature, Lond.*, **166**, 677.
Race, R. R. (1942). *Ann. Eugen., Lond.*, **11**, 365.
Singer, K., and Fisher, B. (1953). *Blood*, **8**, 270.
Thomas, A. T. G., Robertson, G. I., and Davey, D. G. (1953). *Trans. roy. Soc. trop. Med. Hyg.*, **47**, 338.
Vandepitte, J. M., and Louis, L. A. (1953). *Lancet*, **2**, 806.
Wells, I. C., and Itano, H. A. (1951). *J. biol. Chem.*, **188**, 65.

In 1950 a mass-miniature-radiography survey was undertaken in Los Angeles County, California. The population concerned numbered over three million, and more than half —1,736,703—responded and were *x*-rayed satisfactorily. This was the largest survey undertaken up to that date in the United States. Abnormalities were found in 67,966 individuals, of whom ultimately 2,404 were classified as tuberculosis suspects. 1,857 previously unknown cases of active tuberculosis were discovered—a rate of 1.08 per 1,000. Among 10,899 cardiovascular suspects the diagnosis of heart disease was confirmed in 3,388, but of these only 697 were previously unknown : the discovery rate for cardiac cases was 0.4 per 1,000. Exactly 3,500 lung cancer suspects were registered. Ultimately neoplasms were confirmed in 329 cases, of which 246 or 0.14 per 1,000 were malignant. (*Los Angeles County-wide Chest X-ray Survey of 1950*, by G. J. Drolet. Published by the Tuberculosis Control Foundation, Los Angeles, 1953.)

THE VARIABILITY OF SICKLE-CELL RATES IN THE TRIBES OF KENYA AND THE SOUTHERN SUDAN

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We have recently completed a survey of the distribution of sickle cells in the blood of 44 tribes and subtribes in Kenya, and 26 in the southern provinces of the Sudan. The results are given in Tables I and II. In a certain number of tribes the ABO blood groups were also done, the results being given in Table III.

In the present communication we wish to stress that, while the sickling phenomenon is very widespread throughout Africa, south of the Sahara the most striking

TABLE I.—*Sickle-cell Trait (Kenya)*

Race	Tribe	Tribal Division	Location	No. Examined	Positive	
					No.	%
Bantu (North-East, Coastal)	Kikuyu	Fort Hall	Nairobi	67	1	2
" "	Teita	Dabida	Wesu	127	0	0
" "	Pare		Taveta	40	2	5
" "	Chagga		Kibo	75	0	0
" "	Taveta		Taveta	154	37	24
" "	Kamba		Machakos	134	2	1
" "	Nyika	Giriama	Malindi	150	16	11
" "	"	"	Ganda			
" "	"	Kauma	Kilifi / Jaribuni	39	4	10
" "	"	"	"			
" "	"	Chonyis	Kaloleni	90	23	26
" "	"	Jibanas	"	119	16	13
" "	"	Rabais	Rabai	48	5	10
" "	"	Ribe	Ribe	50	13	26
" "	"	Kambe	"	78	27	35
" "	"	Digos	Msambweni	50	11	22
" "	"	Durumas	"	68	7	10
" "	Pokomos	Ngatana	Garsen	102	27	27
" "	Boni		Bargoni	81	0	0
" "	Sanya		Witu	61	0	0
" "	"		Adu	68	8	12
Bantu (North Kavirondo)	Maragoli		Majengo	100	9	9
" "	Bunyori		Kimba	100	6	6
" "	Nyangori		Kapsengeri	44	2	5
" "	Kitosh		Bungoma	100	21	21
" "	Kakamega		Kakamegas	50	6	12
" "	"		"	46	0	0
" "	Marama		Buteri	100	10	10
" "	Wangas		Mumias	96	19	20
" "	Kisii (Bantu-Nilote?)		Kericho	100	3	3
Bantu (South-East, Coastal)	Makonda		Porto Amelia	100	40	40
" "	"		Vipinco	50	2	4
E. Hamites	Masai	Kaputei / Lodokelani	Kajiado	100	0	0
" "	"	Purko / Loita	Narok	82	0	0
" "	Galla		Garsen	30	0	0
" "	Kipsigis		Kericho	100	2	2
" "	Somalis	Adjuran		14	0	0
" "	"	Degodia		20	0	0
" "	"	Ogaden		16	0	0
" "	"	Gurren				
" "	Boran	Sakuya		6	0	0
Nilo-Hamites	Turkanas			50	0	0
Nilotes ..	Luo	S. Kavirondo		100	28	28
Mixed Arab-Negro	Bajuns	Lamu		45	1	2
" "	Swahili	Ganda		50	2	4
" "	"	Kakounyi		50	5	10
" "	Arabs	Malindi		61	1	2

TABLE II.—*Sickle-cell Trait (Southern Sudan)*

Race or Language Group	Tribe	Subtribe	Location	No. Examined	Positive	
					No.	%
Nilotic ..	Dinka	Bor	Malek	87	0	0
,, ..	,,	,,	Cattle Post	77	2	3
,, ..	,,	Duk	,, ,,	22	0	0
,, ..	,,	Melut	Melut	20	0	0
,, ..	,,	Toich	Sobat	38	0	0
,, ..	Nuer	Adok	Adok	100	1	1
,, ..	,,	Ler	Ler			
,, ..	Shilluk	Tonga	Tonga	110	0	0
,, ..	,,	Malakal	Malakal	56	0	0
,, ? ..	Mandari	Terakeka	Terakeka	105	18	17
,, ? ..	,,	Tali Post	Tali Post	98	7	7
,, ..	Acholi	Torit	Torit	54	6	11
,, ? ..	Lango	,,	,,	30	1	3
,, ..	Anuak	Lafon	Lafon	96	8	8
,, ? ..	Madi	Opari	Opari	71	13	18
Nilo-Hamitic:						
Bari-speaking group	Bari	Bari (true)	Rejaf	100	7	7
	Fajelu	Fajelu	Lainya	100	9	9
	Kuku	Kuku	Yei	39	3	8
	Kakwa	Kakwa	,,	76	6	8
Bongo-Mittu-speaking group	Baka	Baka	,,	105	9	8
	Moro	Moro	Juba	71	2	3
	Mundu	Mundu	Yei	80	13	16
Lotuku-speaking group	Latuka	Latuka	Lambalua	72	0	0
	Dongotona	Dongotona	Isoke	70	0	0
	Lokoiya	Lokoiya	Liria	98	5	5
Didinga-speaking group	Longarim	Longarim	Wathit Forest	73	1	2
	Logia	Logia	,, ,,	38	0	0
Western Bantu?	Azande		Juba	28	3	11

TABLE III.—*ABO Blood Groups (Kenya)*

Tribe or Subtribe	No. Examined	Distribution Blood Groups (%)			
		A	B	O	AB
Taveta	56	30	22	44	4
Teita	27	41	7	45	7
Jibanas ..	72	22	28	47	3
Chonyis ..	55	22	5	73	—
Kambe ..	77	25	16	57	3
Giriama ..	100	22	26	50	2
Durumas ..	37	24	16	43	16
Kauma ..	27	8	36	56	—
Rabais ..	50	14	20	60	6
Ribe	50	10	10	78	2
Pokomo ..	42	29	26	38	7
Boni	50	6	50	34	10
Sanya (Witu) ..	61	64	2	34	0
,, (Adu) ..	65	23	31	37	9
Bajun	37	30	16	52	2
Swahili ..	98	10	46	35	8
Arabs	61	33	10	54	3

variations are found in its frequency and in that of the ABO blood groups; we also suggest reasons for this variability. Although the rates are based on relatively small samples, the differences noted are statistically highly significant.

We have previously suggested (Foy and Kondi, 1951; Foy, Kondi, and Alexandrides, 1951; Foy, Kondi, and Brass, 1951) that the sickling characteristic cannot be regarded as a peculiarity of the negro race, and that its ethnological significance may have been overrated. The studies reported in this paper seem to substantiate this view, but until further work has been done it is better not to draw any conclusions.

Our work in the Sudan confirmed what we had already found in Kenya and Portuguese East Africa (P.E.A.)—namely, that there are great variations in the percentage of sickling and ABO groups, not only among different tribes but also in subgroups within the same tribe, although such subgroups speak the same language, have the same cultural and social characteristics, and now intermarry freely (Foy and Kondi, 1951, 1952; Foy, Kondi, and Alexandrides, 1951; Foy, Kondi, and Brass, 1951; Foy, Kondi, and Hargreaves, 1952; Foy, Kondi, *et al.*, 1952). These variations may be conveniently classified as follows.

Variability in Sickling Rate

(*a*) Differences between groups of the same tribe, living in different areas, as exemplified by the Mandaris in the Southern Sudan. From Table II it will be seen that the Mandari of Terakeka have a sickle-cell rate of 17%, whilst the Mandari at Tali Post have a rate of only 7%, although both groups speak the same language, are said to be ethnically similar, and are surrounded by Dinkas, whose rate is less than 1%. Similarly, the Makonda in North P.E.A. have a rate of 40%, whilst a group of them who have migrated from P.E.A. for temporary work in Kenya have a rate of 4%. These Makonda all speak the same language, and have the same social and cultural background; both sexes have extensive geometrical tattoo marks on their faces and bodies, and all the women wear the hideous upper-lip plug. The Acholi of Uganda (Lehmann and Raper, 1949) have a sickling rate of 27%, while those of the Sudan have a rate of 11%. The Madi of Uganda have a rate of 3% (Lehmann and Raper, 1949), while those in the Sudan have 18%. The Wasanya of Witu have a rate of nil, those of Adu have 12%.

(*b*) Variations within subgroups of the same tribe living in closely contiguous areas, as among the Nyika, a Bantu-speaking people inhabiting the coastal regions of Kenya. The nine subgroups of this tribe that have been examined for sickling have shown variations from 10% to 35% (Table I), although they occupy locations that abut on each other, speak the same language, and have the same customs and environment. These variations among the Nyika seemed to us so striking that it was decided to take further samples to check the results. Every care was taken to ensure that only the parents and one member from each family were examined, as the examination of "family groups" might have added to the variability and thus have led to differences which were apparently significant but in fact not so. The results of the second survey agreed so closely with those of the first that the two sets of results were amalgamated in Table I.

(*c*) Variations between different tribes occupying the same area, as shown by the inhabitants of the triangle of country between Voi, Mombasa, and the Kilimanjaro foothills. In this region there reside several different Bantu-speaking tribes, the Kamba, Teita, Pare, and the Chagga, none of whom, as will be seen from Table I, have sickling rates above 5%. Yet in the centre of these groups of people are the Taveta, who have a rate of 24%. Another example is found in the Galla, Pokomo, and Boni. The two former occupy the right and left banks of the Tana River, the Boni the area adjacent to the Pokomo. The sickling rates for these three are nil, 27%, and nil respectively.

It may also be noticed that the Anuaks of the Sudan, at Lafon Hill, generally regarded as Nilotic and related through the Acholi to the Luo, have a rate of only 8%, indicating that their affinities with the Luo are not as close as generally supposed on a linguistic basis.

It occurred to us that since the sickling rate showed such great variability this might also obtain for the ABO blood groups. Samples were therefore taken in a number of tribes, particularly amongst the Nyika subtribes, and the results are given in Table III. From this it is evident that variability also exists in the frequencies of the ABO blood groups, notably among the Sanyas of Witu and Adu, as well as in the Nyika as a whole.

Causes of the Variability

The causes of this great variability within tribal groups is difficult to explain, and we suggest the following possibilities:

1. All the evidence available indicates that the genetical hypothesis explains the inheritance of sickling in the great majority of cases and that the incidence of sickle-cell anaemia is more likely to be correlated with high incidence of sickle-cell trait than with

any admixture of Caucasian blood as suggested by Lehmann and Raper (1949). We think, however, that the simple homozygous-heterozygous hypothesis may not take into consideration all the known facts, since it is not uncommon to find cases of sickle-cell anaemia, only one of whose parents have the trait, or only one the anaemia. It should, however, be remembered in this connexion that daily variations sometimes occur in the sickling of the same individual, especially in the trait condition, for reasons which at present are not clear. Further, we have noticed in our surveys that some individuals may have large numbers of sickle cells, whilst in others only one or two characteristic sickle cells can be found in the whole film. In view of this, it is possible that internal or external environment has some effect on the manifestation of the condition. However, since wide variations are found between tribes and subtribes occupying apparently similar external environments, this possibility appears to us to be rather unlikely, and, so far as we are aware, external environment has not been shown to effect the frequencies of ABO groups, yet similar variations occur, as with sickling.

2. Intermarriage of neighbouring tribes with different rates in certain areas might produce groups with rates intermediate between them. If this were an important factor, then one would expect it to operate in the subgroups of the same tribe living under similar conditions and related geographically and culturally. Thus, the Mandari of Tali Post, who might originally have had a high sickling rate, could have intermarried with the low rate Dinkas, yet similar Mandari of Terakeka, also surrounded by similar Dinkas, have a high rate. The Nyika subtribes living in the same location and in the closest proximity have very different sickling rates. For example, the contiguous Durumas and Digos have rates of 10% and 22% respectively, and, similarly, the rates for the Ribe and Jibanas are 26% and 13%.

It is also difficult to imagine how intermarriage could have caused differences as large as those found. For example, among the Makonda, where the rates in the two subgroups are 4% and 40%, the original racial strain with a high sickling rate must, on this hypothesis, have been diluted, in the low-rate group, to one-tenth by intermarriage, and have very little "Makonda" left in it.

In addition, if racial or tribal mixtures were the complete explanation of the variability, we would expect differences in the blood-group frequencies to be associated with the sickling rate, but this does not occur, as will be seen from Table III. For example, a low frequency of the B blood group is associated with a high sickling rate among the Chonyis and Ribe, but with a low rate of sickling among the Sanya of Witu.

3. If sickle-cell anaemia often causes death among Africans before the reproductive period, how is it that the trait condition is so common? Our own experience in Kenya is that mortality in the anaemic condition is high, especially in the age group of 0–10 years. This being so, there must be some counteracting factor which prevents reduction in the gene frequency. This maintenance of a high gene frequency may indicate: (1) spontaneous mutations; this would seem unlikely in view of the probable rarity of mutation compared with the rate of mutation necessary to replace the genes lost by death. (2) Heterosis, in relation to reproduction, the heterozygote being more fertile than the homozygote (Boyd, 1950). Although no direct evidence of this is available for the sickle-cell trait, it is perhaps worth while to note that the effect of deaths in young children—or *in utero*—on the gene frequency might not be as large as would be expected, since the African woman would then be able to bear another child at a shorter interval than normally, this being linked with the custom, almost universal in East and Central Africa, of long periods of lactation, during which coitus is prohibited. If hybrid vigour is a factor in the situation, it might be affected by environment, and this would introduce a further source of variation in the incidence of the trait rate. It seems improbable, however, that these considerations could apply to blood-group variations; and if we are searching for a common cause for the variability in the two characteristics (blood groups and sickling), then this suggestion must be ruled out.

4. Genetic drift may be a factor where small groups of people are virtually isolated genetically—that is, they marry almost entirely within their own small group. In such small groups purely chance factors operating over a long period may cause the gene frequency to change greatly. If the population of such a small group then increases, the changed gene frequency will remain fairly stable unless intermarriage or other factors are introduced to upset it. The discussion under intermarriage, above, indicates that inbreeding may have been the rule among the groups examined. Our knowledge of African conditions of living and the effects of famine, epidemics, etc., leads us to suppose that the present tribes and subtribes may have been very small in number at some period in the past. It seems reasonable, therefore, to suppose that conditions suitable for the action of genetic drift may have existed among these tribal groups, and that the variation thus introduced has not yet been equalized by widespread intermixture of tribes. Such genetic drift would affect the genes both for sickling and for blood groups, but each one independently, so that, while variability would follow in each case, there would be no association between the drift for sickling and that for blood groups. The situation that would develop would be precisely that found to exist in our surveys.

In short, it is evident that there are variations in the rate of sickling (*a*) among what are generally regarded as the major African races, such as the Eastern Hamites, with rates below 1%, and the Nilotics and Bantu, sometimes with high rates; (*b*) among individual tribes within the major African races—for example, among the Bantu group of East Africa, such as the Taveta, Kitosh, Pokomo, etc., which have high rates, and the Teita, Chagga, Pare, Boni, etc., who have almost no sickling; and (*c*) between subgroups of the same tribe as described above for the Nyika.

Ethnological Significance

In view of our findings, what can be said regarding the ethnological significance of sickle-cell trait in Africa—or, in fact, about the significance of the ABO blood groups?

It would appear from our results that rates taken from only one group of any particular tribe cannot be regarded as characteristic for the tribe as a whole, nor can the overall rates for a tribe represent the situation in a major African race.

If the hypothesis of genetic drift is applicable, then it follows that the present sickling rate in a tribe or subtribe may not bear much relationship to the frequency of the trait as originally introduced. Rates for individual tribes would therefore have little significance ethnologically. On the other hand, random drift is as likely to increase as to decrease the rates, and averages over a number of different tribes which originally had much the same sickling frequency would tend to approximate to that frequency. It is possible that widespread and detailed information on the sickle-cell distribution might give important ethnological information. Such detailed information is not at present available.

Nevertheless, we feel that some of the results presented here may be of ethnological significance. For example, the widely distributed Nilotes in Central Africa are divided according to sickling rates into two main groups—namely, the Dinka, Shilluk, and Nuer of the Sudan, with very low rates, and the Jaluo, Lango, Alur, and Acholi of Kenya and Uganda, with medium to high rates. We do not think that these differences can be ignored ethnologically, although the languages of the two groups have close affinities. It may be worth noting that the frequency of sickling in the Dinka, Nuer, and Shilluk resembles closely that of the Eastern Hamitic races, such as the Masai, Galla, Turkhanas, etc., as do their pastoral and dietetic habits. On the other hand, the Luo, Lango, and Alur have high sickling rates, and are a predominantly agricultural people, with dietetic habits that are unlike those of the Eastern Hamites.

Unless it has a selective value, the frequency of a gene, appearing by mutation in an isolated population, has a negligible probability of increasing. The sickle-cell gene may have been introduced into Africa from outside, perhaps from the East, either overland or by sea. The sea route seems to be the more likely, considering the high rate among the riverine Pokomos and the Makua and Makonda, and the very low rate among the Eastern Hamites, through whose forebears, if it came overland, the gene would have to pass; and it would have persisted among their present-day descendants. The high frequencies found in certain tribes indicate that the proportion of invaders carrying the gene to the invaded was high.

This relation between the invaders and the original population probably varied from place to place as communities became established; and the variation, together with the influence of genetic drift, could, we suggest, account for the widely different incidences that we have found from tribe to tribe. These differences would persist only if relative isolation continued, and it is generally believed that intermariage is now common and probably always occurred to some extent.

With these facts in mind, it is of interest to note the suggestion of Lehmann (1953) that the sickle-cell condition may have been introduced in Africa and the Mediterranean region by migrating Veddic peoples.

Intermarriage would tend to reduce the variability caused by genetic drift: although variations in A and B frequencies were also found they did not present the sharp contrasts in contiguous areas shown by the sickling trait, and this may suggest that the A and B genes were introduced earlier than the sickling one. The spread of the B gene in Western Europe has been described by Candela (1942), and similar postulates may apply to the diffusion of the sickle-cell trait in Africa.

Conclusion

At present there is little to suggest that the possession of the sickling gene has any selective value, and the A and B blood groups which show similar though unrelated variations to those of the sickling frequency are also believed to have no survival value, although it has recently been shown (Aird *et al.*, 1953) that some correlation exists between carcinoma of the stomach and the A blood group, and between acquired haemolytic anaemia and group O (Hunt and Lucia, 1953). It is not impossible that sickling may be related to hookworm or malaria or other tropical condition, but so far as our studies have gone we have not been able to show any such relationship. Until some such factor is demonstrated it would seem to us that genetic drift is the most probable explanation of the variations in both sickling and the ABO blood groups in Africans.

Summary

The incidence of sickle-cell trait and the distribution of the ABO blood groups in certain tribes in East and Central Africa are reported.

Considerable variation was found in different tribes and even between subgroups of the same tribe, indicating that surveys done on large heterogeneous groups of Africans are unlikely to give useful information.

Possible explanations for this are considered, and genetic drift is suggested as the most likely.

The question of the introduction, maintenance, and spread of the sickling gene in Africans is discussed.

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REFERENCES

Aird, I., Bentall, H. H., and Roberts, J. A. F. (1953). *British Medical Journal*, **1**, 799.
Boyd, W. C. (1950). *Genetics and the Races of Man*. Blackwell, Oxford.
Candela, P. B. (1942). *Hum. Biol.*, **14**, 413.
Foy, H., and Kondi, A. (1951). *Lancet*, **2**, 451, 739.
—— —— (1952). *British Medical Journal*, **2**, 996.
—— —— and Alexandrides, C. (1951). *Trans. roy. Soc. trop. Med. Hyg.*, **44**, 729.
—— —— and Brass, W. (1951). *E. Afr. med. J.*, **28**, 1.
—— —— and Hargreaves, A. (1952). *Trans. roy. Soc. trop. Med. Hyg.*, **46**, 327.
—— —— *et al.* (1952). *E. Afr. med. J.*, **29**, 247.
Hunt, M. L., and Lucia, S. P. (1953). *Science*, **118**, 183.
Lehmann, H. (1953). *Man*, **53**, 9.
—— and Raper, A. B. (1949). *Nature, Lond.*, **164**, 494.

ACUTE RESPIRATORY INFECTIONS IN EMPHYSEMA

AN ACCOUNT OF 118 CASES

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The advances in the physiological and pathological understanding of emphysema have not been paralleled by equal success in its clinical management. There may be three reasons for this. First, chronic bronchitis, without doubt the most important single factor in the production of emphysema, is, because of its ubiquity and apparent benignity, regarded as a tolerable evil; secondly, as a result of this the patients are unlikely to consult the physician in the early stages; and, thirdly, as it is a disease which would seem to be both irreversible and progressive, treatment is unrewarding. Because of these considerations the emphysematous patient in a general hospital is usually seen for the first time when suffering from incapacitating dyspnoea, congestivė cardiac failure, or an acute respiratory infection. The latter, responsible for about 4% of the total admissions to my wards, may cause sudden and serious illness which is eminently treatable. This paper is concerned mainly with this aspect of emphysema. Similar cases have been studied at necropsy by Spain and Handler (1946) and Scott and Garvin (1941). Fulton (1953) emphasizes that chronic pulmonary disease is an important cause of mortality and morbidity in middle-aged men in the industrial area of Manchester. The diagnosis and treatment of acute respiratory infection in emphysema have been discussed by Cardon *et al.* (1951).

Material

Between March, 1947, and May, 1952, 118 patients with long-standing bronchitis and emphysema have been under my care because of acute respiratory illness. In all but one, progressive dyspnoea was a prominent feature. This one patient, a man aged 63, said that he was not short of breath as a rule, but physical examination, response to oxygen therapy, and respiratory function tests all indicated emphysema.

Of the 118 patients (100 men, 18 women), 48 died—41 as in-patients and 7 within one year of leaving hospital. The remainder were alive and well in the summer of 1952.*

Age Groups.—The ages of the patients were 30–39 years, 3; 40–49, 12; 50–59, 39; 60–69, 49; 70–79, 15.

Previous Medical History

A history of bronchitis of more than 10 years' duration was given by 100 of the 118 patients. There can be no doubt, therefore, of its importance in the evolution of emphysema.

Most patients said that their bronchitis began insidiously in the past and guessed at its duration. Some were more definite and chose as landmarks either the first world war or a previous attack of pneumonia. Sixteen males fixing upon the first world war attributed their bronchitis to gassing, yet only one had been admitted to hospital because of it. Their memory was probably playing them false. The same criticism might be applied to those who dated their bronchitis from a long-distant pneumonia. There were, however, others whose pneumonic illness was more recent, but here again caution must be exercised in relying on the patient's memory, as is illustrated by the following case of

*Since this article was submitted for publication a survey made in December, 1953, reveals that 75 patients are now dead, 25 are alive and well, and 18 have not been traced.

a woman aged 72 who said that her chest trouble had begun two years previously, after an attack of bronchopneumonia. She seemed a reliable witness, yet severe emphysema and hypertrophy of the right ventricle were found at necropsy. It is unlikely that the gross pathological changes could have arisen in so short a time. It seems to me more likely that the acute illness brought to her notice symptoms which had existed but had been accepted by her as "normal." It is indeed remarkable how frequently morning cough and sputum, often attributed to smoking, are regarded as "normal." Until we use a more accurate guide than memory I do not think we should accept the statement that emphysema can follow directly on a bronchopneumonic illness (Spain and Handler, 1946; Barach, 1948).

A history of asthma was noted in 27 and a family history of "chest trouble" in 13 cases. Two patients had severe kyphoscoliosis dating from childhood.

History Taking.—The memories of these patients are often clouded during the acute illness, and the spouse or relatives can give more accurate information. Twenty patients seemed to be mentally clear on admission to hospital, yet on recovery they had complete amnesia for the first few days. I make it a rule, therefore, to confirm the history on recovery. Even when the patient is not acutely ill, it is important to check his history with that obtained from his wife or children.

Clinical Course

I can best illustrate this by recounting in full the following case.

A metal polisher aged 43 was first seen by me on January 18, 1949. At 12 years of age pneumonia left him with a "weak chest." At 19 he stopped playing football because of exhaustion. At 21 annual winter visits to the doctor for cough medicine began. At 26 "double pneumonia" laid him up for five months, and after this his health deteriorated. At 33 bronchitis was present in the summer as well as the winter. At 38 dyspnoea was burdensome. At 40 he was admitted to this hospital (February 1, 1946) extremely ill with a right upper lobe pneumonia; he was discharged on March 3. On January 18, 1949, when aged 43, five days of bronchitis and pleurisy resulted in such a degree of respiratory embarrassment that emergency admission to hospital was necessary. His doctor wrote: "His sputum is rusty. His temperature is not much raised, but this fact was also noted on his previous admission."

On examination he was mentally clear, but very cyanosed, and had the "frog-like" eyes mentioned by Spain and Handler. His sputum was thick and creamy. Examination of the chest revealed evidence of emphysema and universal moist sounds. There was no clinical or radiological evidence of consolidation. The fundi showed papilloedema and the C.S.F. pressure was 330 mm. There was no sign of congestive cardiac failure. The blood pressure was 120/70. Blood count: haemoglobin 78%; red cells, 4,500,000 per c.mm.; white cells, 17,300 per c.mm. (neutrophils 75%). The alkali reserve was 86 vols.%. Sputum culture yielded haemolytic and non-haemolytic streptococci. Screening and electrocardiography confirmed emphysema and hypertrophy of the right ventricle, and it was noted that there was apical fibrosis with drawing up of the lung roots.

He quickly recovered, and on February 28, in the follow-up clinic, declared himself a different man. He was taking ephedrine and having breathing exercises. On holiday in July he could walk five miles at a brisk pace. One further attack of bronchitis on October 31 necessitated hospital admission, but he quickly recovered. During the summer of 1950 his dyspnoea was more severe, but he could walk one to two miles each day to and from work. Between the summer and autumn of 1950 his ankles swelled intermittently and he was able to do light work only. His head became "thick" and he could not read small print. He felt "rough" at times and fell asleep on the lavatory. After an exacerbation of bronchitis with haemoptysis he was admitted on October 23, 1950. There were signs of congestive cardiac failure; oxygen therapy made him drowsy but he recovered satisfactorily.

His last admission was on January 8, 1951, after an attack of bronchopneumonia. He was extremely dyspnoeic, very cyanosed, drowsy but not oedematous, and complained of spots in front of his eyes when he coughed. There were irregular clonic movements involving the upper limbs and even the trunk. His wife had noticed these twitching movements of the arms and legs in bed for some time. He refused to stay in the oxygen tent because he thought he might die in it. Inhalation of oxygen by the B.L.B. mask caused mental confusion and exaggeration of the clonic movements without relief of the cyanosis. We therefore tried to increase his ineffective minute volume by means of a Paul-Bragg respirator, but could not gear the machine to his respiratory rate. Towards the end he sweated profusely and had cold cyanosed extremities suggesting peripheral circulatory failure; in this state he died on January 11, 1951.

At necropsy the lungs showed marked emphysema and basal bronchopneumonia. There was hypertrophy of the right ventricle, but not of the left, and the wall of the pulmonary artery was as thick as that of the aorta. The smaller branches of the pulmonary artery stood out from the cut surface of the lung, but were free from atheroma. The cerebral and choroid veins were greatly dilated, and the brain showed congestion of the grey and white matter.

Comment.—Although this history represents the typical course of the disease there are several further points which need emphasis. Firstly, the time interval between the onset of the acute respiratory infection and drowsiness, irrationality, and even coma may be short indeed. In fact, these mental symptoms may be the first indication of such an infection. Secondly, the height of the temperature is no guide to the severity of the respiratory infection, since in most cases it is either within or only slightly above the normal range. However, the absence of pyrexia may be more apparent than real, as on recovery the temperature is always subnormal. Finally, some patients present with recurring attacks of congestive cardiac failure without any obvious acute respiratory infection as a precipitating factor. Perhaps antibiotics, in curing repeated acute respiratory infections in these patients, can so prolong life that chronic congestive cardiac failure as a result of emphysema is being seen (Christie, 1952; Whitfield, 1952).

Clinical Picture on Admission to Hospital

Three fairly distinct clinical pictures may be seen, depending on the mental state, degree of cyanosis, and physical signs in the lungs.

Acute Bronchiolitis.—The cyanosis is intense, and to one's surprise the abnormal physical findings in the lungs are few; consisting of scattered rales and rhonchi heard principally at the lung bases, without any evidence of consolidation. Six cases presented with this clinical picture.

Pneumonia.—The cyanosis is less intense than in acute bronchiolitis and the abnormal physical signs are greater. An impaired percussion note, together with scattered areas of bronchial or bronchovesicular breath sounds and rales, is found usually at the lung bases. Bronchopneumonia was encountered in 102 patients and lobar pneumonia in 10.

Acute Psychosis.—Hallucinations dominated the clinical picture in two cases and paranoia in one case. In all three the sole abnormality in the lungs was the presence of abundant rales and rhonchi. In one only was papilloedema seen, and that not marked.

A man aged 56 was pensioned from the police force in 1945 because of chest trouble. During the week before admission he had had acute bronchitis and had been "fuddled" in his head. He was suspicious of the doctors and refused to be examined or treated. His mental state was such that he had to be transferred to the mental observation ward of the North Middlesex Hospital, where he died, in coma, after two days. Post-mortem examination showed severe emphysema and a marked cerebellar pressure cone. (This coning was noted in the other two cases.)

Complications

Mental.—When the cyanosis is intense the patient may be euphoric and ignorant of the seriousness of his illness. This was observed in three cases in this series. The clinical

picture may be complicated by drowsiness (8 cases), confusion (10 cases), irrationality (10 cases), or coma (2 cases). These mental symptoms are very commonly seen as a result of oxygen therapy.

Cardiovascular.—When the acute respiratory infection produces, as it often does, a severe degree of anoxia, the heart may temporarily enlarge (Ferrer *et al.*, 1950). This is clearly shown in Fig. 1. This patient, a man aged 72, was

FIG. 1. FIG. 2.

FIG. 1.—Tracing from *x*-ray film taken on March 25, when the patient, a man aged 72, was extremely cyanosed owing to bronchiolitis. FIG. 2.—Tracing from film taken on May 7 on recovery. Note diminution in size of heart.

admitted on March 19, 1947, with emphysema, bronchiolitis, extreme cyanosis, congestive cardiac failure, and moderate labile hypertension. The recession in heart size after six weeks is shown in Fig. 2. Five years later the heart size remained the same. Each respiratory infection must therefore place a burden on the heart already embarrassed by pulmonary hypertension. Congestive cardiac failure may result. It was encountered either on or shortly after admission in 42 patients, and of these 26 died (3 after discharge from hospital after intervals of nine days, five months, and six months). This is in agreement with the findings of Parker (1940), Spain and Handler (1946), and Fulton (1953). The patients who recovered have been in good health for periods varying from four months to five years. Sinus rhythm was present in all except five patients who had auricular fibrillation. Gallop rhythm was recorded twice. Hypertension was noted in 25 patients, and in three of these the blood pressure was normal in hospital and was observed to be raised only when they attended as out-patients. The blood pressure may be low in patients who are severely anoxic, but this does not seem to influence the prognosis.

Polycythaemia.—Hurtado *et al.* (1945) and Wilson *et al.* (1951) comment on the infrequency of polycythaemia and the frequency of increase in mean corpuscular volume in emphysematous subjects. Wilson *et al.* attribute the latter finding to anoxia. In the present series red-cell counts were done in 32 cases; in 24 the count was less than 5.5 millions, in 6 between 5.5 and 6 millions, and in two above 6 millions. The haemoglobin was determined in 39 cases; in 21 it was 14.8 g.% or less, in 8 it was between 14.8 and 16.2 g., and in 9 between 16.2 and 17.8 g. The mean corpuscular volume was measured in 23 cases; in 9 it was in the range of 78–94 μ^3 and in 14 above this range. As the anoxia was relieved so the mean corpuscular volume fell, but not necessarily to within the normal range. Wilson *et al.* say that the marked polycythaemia which may be seen in emphysema is often associated with severe anoxia and right heart failure. In the present series, of the eight patients with red-cell counts above 5.5 millions, four had congestive cardiac failure.

Sudden Death.—This may occur for no obvious reason, and post-mortem examination may be unhelpful (Brill, 1939; Scott and Garvin, 1941; Spain and Handler, 1946). In this series sudden death with no obvious cause at post-mortem examination occurred on five occasions.

Respiratory Arrhythmia.—On two occasions I have observed that the respirations were irregular both in rhythm and in depth.

Accompanying Diseases.—Carcinoma of the lung was noted twice, angina of effort twice, coronary infarction twice, mitral stenosis once, pericarditis as a complication of lobar pneumonia once, peptic ulcer twice (once with haemorrhage), and carcinoma of the prostate once.

Diagnosis

The diagnosis of emphysema in these patients was relatively easy. Two observations from the foot of the bed are, in my opinion, very suggestive. First, a poor temperature response in the presence of an acute respiratory infection; and, secondly, mental symptoms in an oxygen tent. At the bedside there are two further aids—the fundal appearances (see below) and the fall in the systolic blood pressure on inspiration, which persists even on full recovery. If the blood-pressure cuff is not deflated slowly this finding may be missed. On examination of the chest the three most reliable findings are the equally low position of both leaves of the diaphragm, absence or diminution of tidal percussion (most readily demonstrated on the right side because of the presence of the liver), and poor basal air entry. A non-emphysematous thin person with a long chest may give the impression that the diaphragm is low, but here the basal air entry is good.

Fundi.—In many cases of emphysema the fundi are normal. However, the appearances in advanced emphysema with cyanosis are, in my opinion, characteristic and are unrelated to the presence or absence of polycythaemia. The retina is darker in colour than normal. This is due to anoxia, since it is relieved by full oxygenation. The veins are dilated beyond the usual vein-to-artery ratio of 3:2; they are tortuous and much darker than usual. One must be cautious in interpreting these appearances, since the temporal branches of the retinal vein normally look very full, and experience alone can decide what is abnormal. In cases showing dilatation and tortuosity of the veins the arteries too may be dilated and even tortuous.

In the presence of an acute respiratory infection these appearances are accentuated, and changes in the nerve head may be seen. The papillae may be oedematous or merely pinkish. When examination of the nerve head leaves one in doubt regarding the presence or absence of papilloedema, help may be obtained by observing the venous pulsation therein. If venous pulsation is present spontaneously or is induced after only light pressure on the globe, then it is unlikely that papilloedema is present (Walsh, 1947). Papilloedema was seen in eight patients, and only one of them had polycythaemia. I have previously reported three cases of severe emphysema with papilloedema, but without polycythaemia, which are not included in this series (Simpson, 1948). As the acute respiratory infection subsides, so the papilloedema and other changes regress.

As these patients come into the advanced age group arteriosclerotic retinitis may also be seen.

Differential Diagnosis

Although the diagnosis of these cases is usually easy, difficulty may arise, since an acute respiratory infection may precipitate failure in an overburdened left ventricle. In older people, in whom the presenting symptom is dyspnoea, and who have a raised temperature and moisture in the lungs with some of the physical signs of emphysema, it may be difficult to decide whether the condition is due to emphysema with an added respiratory infection or to left ventricular failure. If the fundal appearances described above are present then one can diagnose emphysema with assurance. A short history of dyspnoea, with little antecedent chest trouble, moderate cyanosis, normal or arteriosclerotic fundi, and an immediate response to intravenous aminophylline, favours left ventricular failure.

Post-mortem Findings

Thirty-six post-mortem examinations were done on 41 patients who died in hospital.

Lungs.—Both emphysema and pleural adhesions of greater or less degree were always found. An acute bronchiolitis

or pneumonia was seen in all except those dying suddenly and unexpectedly. Pulmonary oedema was often observed.

Heart.—The heart was studied in 30 cases. Measurement of the thickness of the muscle wall was not regarded as an accurate method of assessing ventricular hypertrophy. Without previous fixing, the weight of the free wall of each ventricle, together with a portion of the septum, as in Herrmann and Wilson's (1922) method, was determined. Although we cannot claim that our results show the accuracy of Lewis's (1914) method, they confirmed the visual impression of right ventricular hypertrophy in every case. The ratio of the weight of the left ventricle to that of the right, determined as above, was 1.2 to 1 or less in all except three cases, and in each of these systemic hypertension was present.

Pulmonary Artery.—Atheroma of the main trunk or of the smaller branches was noted in 12 cases, and its degree bore no relation either to the severity of the emphysema or to the size of the right ventricle. This is in agreement with the findings of Parker (1940). At necropsy on one case the right ventricle weighed 320 g. and the pulmonary artery was larger in diameter than the aorta, yet atheroma was limited to the main trunk of the pulmonary artery. However, in most cases the smaller branches of the pulmonary artery were much less translucent than normal, indicating fibrosis of the walls.

Brain.—In cases in which severe anoxia was present, but more especially after death in an oxygen tent, the cerebral venous system was very congested. This vascular congestion was seen in the grey and white matter, and in most cases the choroid and internal cerebral veins were very conspicuous. Venous oozing was seen in two cases—once into the lateral ventricle and once into the surface of the brain. The cerebral ventricles were not dilated, nor were the convolutions flattened.

Cerebellar Pressure Cone.—A marked cerebellar pressure cone was seen in four cases, three dying with psychotic symptoms and one dying suddenly and unexpectedly without mental symptoms. This is presumably due to the raised cerebrospinal fluid pressure which occurs in severe emphysema, as a result of the disturbance in blood gases, and may cause papilloedema (Simpson, 1948).

Treatment

This can be divided into two sections: treatment of the acute respiratory infections necessitating admission to hospital and treatment on recovery.

(a) Acute Respiratory Infection

Barach (1948) says that an acute respiratory infection in an emphysematous subject should be treated as an emergency, and with this I wholly agree. I would like to re-emphasize that a low oral temperature, if the patient can keep his lips closed, does not necessarily mean that the infection is a slight one.

We find that the majority of these respiratory infections respond to penicillin, which can be given either as procaine penicillin G, 300.000 units, or as penethamate hydriodide ("estopen"), 500.000 units, once or twice daily, depending on the severity of the infection. If a response to penicillin is not obtained, chloramphenicol is usually effective; and, in cases not responding to either of these, sensitivity tests done on sputum cultures will indicate the appropriate antibiotic.

From the general practitioner's standpoint certain events make hospital admission imperative: (1) persistence of a raised temperature in spite of treatment; (2) severe infection as indicated by intense cyanosis, drowsiness, muscular twitching, irrationality, acute psychosis, or coma; and (3) congestive cardiac failure.

Mental symptoms, seen especially after oxygen therapy, may require sedation, and it is important to remember that morphine is lethal to these patients. Barbiturates, too, are better avoided. Paraldehyde, 5 ml. intramuscularly and repeated if necessary, seems to be the best sedative to use.

Antispasmodics are of little use to the acutely ill patient, but if progress is delayed or if relapse should occur the combined use of postural drainage and antispasmodics may be very effective in promoting recovery.

Oxygen Therapy

Mental symptoms or even coma may ensue when oxygen is given to these patients, especially the very anoxic ones (Richards, 1950). Studies at this hospital suggest that the mental symptoms are due to carbon dioxide narcosis, but other theories have been advanced and discussed (Comroe *et al.*, 1950; Mithoefer, 1952). However, I agree with Barach (1948, 1950b) that the occurrence of these untoward symptoms should not deter us from continuing with oxygen therapy, although nursing may be difficult. In the present series mental symptoms or coma were seen in 49 patients, and 17 of them died (see Table).

Mental Symptoms During Oxygen Therapy

Year	Total Admissions	No. Treated	Mental Symptoms or Coma	Died
1947	10	6	2	0
1948	14	6	5	3
1949	20	6	4	2
1950	20	12	9	5
1951	41	27	20	4
1952	13	13	9	3

Oxygen may be given by nasal catheter or tent (Simpson, 1936). The patients included in the table were so severely ill that it was thought advisable to put them at once into an oxygen tent, and they were left in even though mental symptoms or coma supervened. Although this procedure was far from ideal, I am convinced that more lives were saved than lost by this means.

As an alternative Barach (1948) advises that if the patient is severely anoxic, and hence more prone to carbon dioxide narcosis, oxygen should be given initially by nasal catheter at a rate of, say, 3 litres a minute, and the rate of flow *gradually* increased. He suggests that when the patient is acclimatized to a high concentration of oxygen in the inspired air then a tent can replace the catheter. He does this to avoid a rapid rise of arterial carbon dioxide, with consequent lowering of the arterial *p*H which occurs in the tent and which, he thinks, is the cause of the coma rather than the raised arterial carbon dioxide itself. In other words, patients can tolerate a high arterial carbon dioxide if it is *gradually* produced (Barach, 1950a).

I have, more recently, used this method in severely ill and disorientated patients and have avoided coma, which, I feel sure, would have supervened had they been put at once into an oxygen tent. I therefore now use Barach's method in every case except those in which urgency demands the use of an oxygen tent. Coma in the tent is by no means necessarily fatal. Even if the patient dies in the tent, it must be remembered that the severity of the infection, the duration and degree of the anoxia, and the cardiac status all have an important bearing on the immediate prognosis.

My instructions to the nursing staff when the nasal catheter is used (preferably Tudor Edwards spectacles) are to watch for coma and not to worry about the relief of the cyanosis. If coma supervenes then the rate of flow of oxygen must be reduced.

Mental symptoms or coma are not commonly seen after oxygen therapy in the less cyanosed, less ill case, and a tent may be used from the beginning.

The use of antibiotics, by clearing the bronchial tree, lessens the anoxia and therefore the complications of oxygen therapy. When the patient remains in coma in the oxygen tent and the condition becomes grave the use of a respirator has been recommended (Boutourline-Young and Whittenberger, 1951). When I have used the tank or cuirass type of respirator I have found, like them, that the respirator cannot be set to the rhythm of the patient's functioning but depressed respiratory centre, and that therefore it is of little assistance.

(b) After-treatment

After recovery, I attach the greatest importance to the mental outlook of the patient. He should be made to feel that he is not just a "chronic bronchitic" for whom nothing can be done. He should be able to apply at any time for advice or treatment and attend the clinic at least at six-monthly intervals in the autumn and spring. Enthusiasm in treatment also helps a lot in getting his co-operation and confidence.

The patient should stay indoors in foggy weather and avoid, so far as is possible, direct contact with people who have an upper respiratory tract infection. The relatives must be told to look out for signs of trouble, such as drowsiness and muscular twitching, and report them at once to the doctor. If the patient should have a chest infection he should go at once to bed in a warmed room. This is important, since I have repeatedly had patients relapse who went from the centrally heated atmosphere of the hospital to the cold conditions of the home.

Breathing Exercises.—Diaphragmatic and other breathing exercises are taught routinely, but, unfortunately, patients often forget to do them at home. There is no doubt of their value. After the breathing has been improved by these exercises I use a modification of a method described by Reed (1952). First of all the positions of the head and body on expiration and inspiration are demonstrated. On expiration the head is flexed, the spine bowed, the body and arms relaxed; and on inspiration the head is extended, the chin tucked in, and the spine extended. The patient then breathes in and out as deeply as he can, assuming these positions at the end of inspiration and expiration. Next he walks, continuing to breathe in this fashion. He finds that he takes so many steps to each inspiration and so many to each expiration. He is then told to continue walking and breathing like this on discharge from hospital.

Antispasmodics

Ephedrine, being undoubtedly the drug of choice, was prescribed routinely, and only 11 patients did not tolerate it, usually owing to its effect on micturition. I start with ¼ gr. (32 mg.) t.d.s. and increase by ¼ gr. daily to the limit of tolerance, as judged by difficulty in micturition, tremor, or nausea. No symptoms referable to the cardiovascular system were observed. When this point has been reached the daily dose is reduced by ¼ gr. (32 mg.) or more, so that toxic symptoms do not continue, and I give it during the week, but not at week-ends (Herxheimer, 1946). One of my patients says he is much worse if he does not take it continually, and another finds that 1 gr. (65 mg.) before bedtime ensures a good night's rest. Often I give the ephedrine in a freshly prepared mixture containing phenobarbitone soluble, ½ gr. (32 mg.), syrup of codeine phosphate, 30 minims (1.8 ml.), in stramonium and potassium iodide mixture (*B.P.C., N.F.*, 1952) or mixture of creosote and potassium iodide (*B.P.C.*).

Hypertension does not contraindicate the use of ephedrine. In my experience aminophylline is very inferior to ephedrine and less well tolerated, and I use it only in patients with severe bronchial spasm. In these it is most useful administered as a 0.5-g. suppository at night. Aerosol inhalations of adrenaline, phenylephrine, or isoprenaline produce fleeting benefit, and also are of greatest use in the asthmatic patients. Inhalation of oxygen alone will often relieve the dyspnoea of the emphysematous patient. Therefore, in attempting to assess the value of any inhaled antispasmodics, it is essential that the gaseous part of the aerosol should be *air and not oxygen*. Isoprenaline, 10 or 20 mg., sucked under the tongue may be of benefit in the ordinary case of emphysema, but the side-effects of palpitation, headache, and tremor often preclude its use.

For control of the cough at night I use codeine phosphate, ½–1 gr. (32–65 mg.), or codeine linctus (*B.P.C.*), 60 minims (3.6 ml.). For headache I find caffeine citrate, 10 gr. (0.65 g.), effective. There is no doubt that those who smoke are improved if they can stop it. Following the observation of Whiteside and Coigley (1952), I have used hexamethonium bromide in one case only, but without benefit.

(c) Congestive Cardiac Failure

In this series, 42 patients had sacral or ankle oedema, either on or after admission. Of these, 26 died (three after discharge from hospital). After control of the respiratory infection the oedema often subsides. If, however, this persists, it may be treated with digitalis, low-salt diet, and mercurial diuretics. There is, as in the rheumatic heart case, a "point of no return" beyond which oedema remains in spite of all drugs, and then acupuncture brings temporary relief. I have had to perform this only once.

Summary

During the past five years 118 emphysematous patients with an added respiratory infection were admitted as emergencies under my care. Forty-five died. Although congestive cardiac failure might complicate the issue, as it did in 42 patients, 26 of whom died, for the most part three clinical pictures were presented: acute bronchiolitis with its accompanying acute anoxia; pneumonia; and, rarely, a psychotic state. The first two groups could be complicated by mental symptoms, especially after oxygen therapy. The presence of a marked cerebellar pressure cone was noted at necropsy in three psychotic patients. Of the 70 patients given oxygen therapy, 49 had mental symptoms or lapsed into coma, and 17 of them died: it is emphasized that in the most severely ill cases oxygen therapy should be continued in spite of these untoward symptoms. However, for the safer administration of oxygen the reasons for using a nasal catheter as against a tent are discussed.

Study of the natural history of emphysema shows that the outlook is not good, many patients dying in the sixth and seventh decades or even earlier, and they are often incapacitated before this in the wage-earning period of life. The clinical diagnosis of emphysema is discussed, and the diagnostic value of the fundal appearances is emphasized.

I wish to thank the sisters, nursing staff, and my house-physicians for their unfailing help in this study. I am indebted to Dr. J. T. Prendiville for the post-mortem examinations done at this hospital and to Dr. J. F. Heggie for the one done at the North Middlesex Hospital. Finally, I wish to thank Dr. J. G. Scadding for his great help in the preparation of this paper.

BIBLIOGRAPHY

Barach, A. L. (1948). *Physiologic Therapy in Respiratory Diseases*, 2nd ed. Lippincott, Philadelphia.
—— (1950a). *J. Amer. med. Ass.*, **143**, 1047.
—— (1950b). *Bull. N.Y. Acad. Med.*, **26**, 370.
Boutourline-Young, H. J., and Whittenberger, J. L. (1951). *J. clin. Invest.*, **30**, 838.
Brill, I. C. (1939). *Ann. intern. Med.*, **13**, 513.
Cardon, L., Lemberg, L., and Greenebaum, R. S. (1951). Ibid., **34**, 559.
Christie, R. V. (1952). In *Diseases of the Chest*, edited by G. Marshall and K. M. A. Perry, **2**, 101. Butterworth, London.
Comroe, J. H., Bahnson, E. R., and Coates, E. O. (1950). *J. Amer. med. Ass.*, **143**, 1044.
Ferrer, M. I., Harvey, R. M., Cathcart, R. T., Webster, C. A., Richards, D. W., jun., and Cournand, A. (1950). *Circulation*, **1**, 161.
Fulton, R. M. (1953). *Quart. J. Med.*, **22**, 43.
Herrmann, G. R., and Wilson, F. N. (1922). *Heart*, **9**, 91.
Herxheimer, H. (1946). *British Medical Journal*, **1**, 350.
Hurtado, A., Merino, C., and Delgado, E. (1945). *Arch. intern. Med.*, **75**, 295, 315.
Lewis, T. (1914). *Heart*, **5**, 367.
Mithoefer, J. C. (1952). *J. Amer. med. Ass.*, **149**, 1116.
Parker, R. L. (1940). *Ann. intern. Med.*, **14**, 795.
Reed, J. M. W. (1952). In *Diseases of the Chest*, edited by G. Marshall and K. M. A. Perry, **2**, 395. Butterworth, London.
Richards, D. W., jun. (1950). *Bull. N.Y. Acad. Med.*, **26**, 384.
Scott, R. W., and Garvin, C. F. (1941). *Amer. Heart J.*, **22**, 56.
Simpson, T. (1936). *Univ. of Leeds Med. Soc. Mag.*, **6**, 123.
—— (1948). *British Medical Journal*, **2**, 639.
Spain, D. M., and Handler, B. J. (1946). *Arch. intern. Med.*, **77**, 57.
Walsh, Frank B. (1947). *Clinical Neuro-ophthalmology*. Williams and Wilkins, Baltimore.
Whiteside, J. D., and Coigley, M. H. (1952). *Lancet*, **2**, 1037.
Whitfield, A. G. W. (1952). *British Medical Journal*, **2**, 1227.
Wilson, R. H., Borden, C. W., and Ebert, R. V. (1951). *Arch. intern. Med.*, **88**, 581.

RAISED INTRACRANIAL PRESSURE IN EMPHYSEMA

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The cerebrospinal-fluid pressure is usually normal in emphysema, but during intercurrent acute respiratory infections symptoms and signs of raised intracranial pressure—headache, blurred vision, papilloedema—not infrequently develop (Simpson, 1948). The observations recorded in this paper throw light on the aetiology of the raised intracranial pressure found in these circumstances. The relationship of intracranial hypertension to mental disturbance occurring during oxygen therapy is discussed.

Experimental Subjects and Method

Lumbar puncture was performed in a series of 12 emphysematous patients (including 3 with papilloedema) suffering from an acute respiratory infection: in 8 immediately following admission to hospital, and in 4 after 4 to 80 hours of oxygen therapy in a tent. In these four patients relief of anoxia was maintained during lumbar puncture by inhalation of 100% oxygen via a B.L.B. mask. In view of the observations of Friedfeld and Fishberg (1934) and Pickering (1934) of the effect of increased jugular venous pressure and severe hypertension in causing raised intracranial pressure, none of the patients studied had either of these complications. The C.S.F. pressure was measured in the horizontal position with a glass manometer (internal bore 2 mm.) calibrated up to 700 mm. The effect of muscular tension and apprehension was eliminated so far as possible by recording pressures at intervals of 30 seconds for 10–30 minutes until a stable basal level was obtained. It was found that when the C.S.F. pressure was within normal limits fluctuations were seldom greater than 20–25 mm. (Fig. 1), but when it was elevated spontaneous fluctuations of much greater magnitude could occur, and a true estimate of the basal pressure might be obtained only after 30 minutes' recording (Fig. 3). Blood was obtained for measurement of oxygen saturation and carbon dioxide content by arterial puncture immediately before lumbar puncture.

Raised Intracranial Pressure in Emphysematous Subjects with Acute Respiratory Infections

Case	C.S.F. Pressure	Arterial O_2 Saturation (%)	Plasma CO_2 Vols.%	Inspired Gas	Comment
1	500–600	40	91	Air	Papilloedema present on admission
	160	83	78	,,	On recovery 15 days later
2	420–460	—	75·1	,,	Deeply cyanosed and disorientated
	160–180	72	75·4	,,	On recovery 12 days later
3	300	52	72	,,	Disorientated and restless
4	360	67·4	79·3	,,	On admission
5	320–360	68·4	95·8	,,	,, ,,
6	270–300	—	—	,,	Bilateral papilloedema; B.P. 160/100; J.V.P. +6 cm. on admission
	420–440	—	—	,,	
	220–260	89	83	Air	27 days after admission
7	280	—	85·5	,,	Moderate cyanosis
8	165–190	69·7	56·2	,,	Plasma CO_2 63 vols. on recovery
9	285–305	94	100	O_2	L.P. after 80 hours' O_2 therapy
	150–160	92·6	64	Air	On recovery
10	300	100	102·5	O_2	Papilloedema present
11	250	94·8	84·3	,,	L.P. after 16 hours' O_2
12	170–200	—	91·5	,,	,, ,, 4 ,, ,,

Details of the C.S.F. pressure, arterial oxygen saturation, and arterial plasma carbon dioxide content are recorded in the Table. In 10 of the 12 subjects C.S.F. pressures above the normal upper limit of 200 mm. were observed, with pressures of over 350 mm. in five. Arterial anoxaemia was present in all cases (O_2 saturation 40–89%) and hypercapnia (plasma carbon dioxide content>66 vols.%) in all except one.

Effect of Anoxia and Hypercapnia on C.S.F. Pressure

The exclusion of patients with raised venous pressure and hypertension narrowed the possible causes of raised intracranial pressure. The almost invariable presence of anoxia, hypercapnia, and dyspnoea suggested that a study of the effects on C.S.F. pressure of breathing pure oxygen, low oxygen and high carbon dioxide mixtures, and of hyperventilation might prove fruitful.

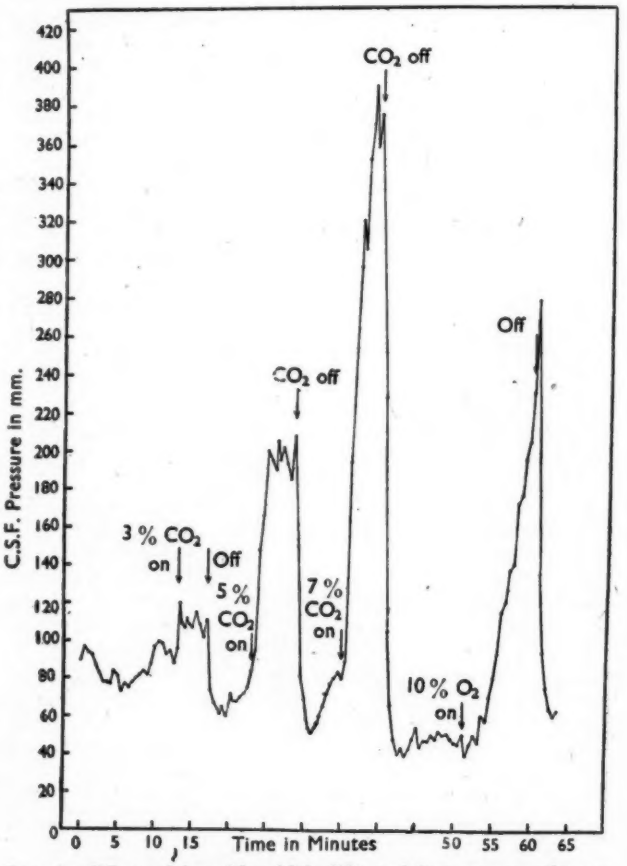

FIG. 1.—Effect of breathing high CO_2 and low oxygen mixtures on C.S.F. pressure in a patient with syphilitic aortitis.

Fig. 1 illustrates the effect of breathing various gas mixtures in a 49-year-old patient with syphilitic aortitis. With 3, 5, and 7% carbon dioxide in oxygen inhaled for five to seven minutes the C.S.F. pressure rose by 27, 133, and 310 mm. respectively. With 10% oxygen in nitrogen the inhalation was terminated before the pressure had finished rising, as the patient became deeply cyanosed and complained of severe headache. Voluntary hyperventilation will consistently produce a fall of 30–50 mm. in C.S.F. pressure (presumably due to washing out carbon dioxide), and if muscular movement has any effect in raising the pressure it is completely outweighed by the effect of hypocapnia and alkalosis. The combined results of inhalation of various combinations of

*British Medical Association Ernest Hart Memorial Scholar, 1952.

carbon dioxide in 29 subjects is presented in Fig. 2. The scatter of individual observations is considerable, especially with the higher concentrations of carbon dioxide. For 3, 5, and 7% CO_2 the mean increases in pressure were 50, 130, and 280 mm. There was no correlation between the magnitude of the rise in C.S.F. pressure on inhaling carbon dioxide

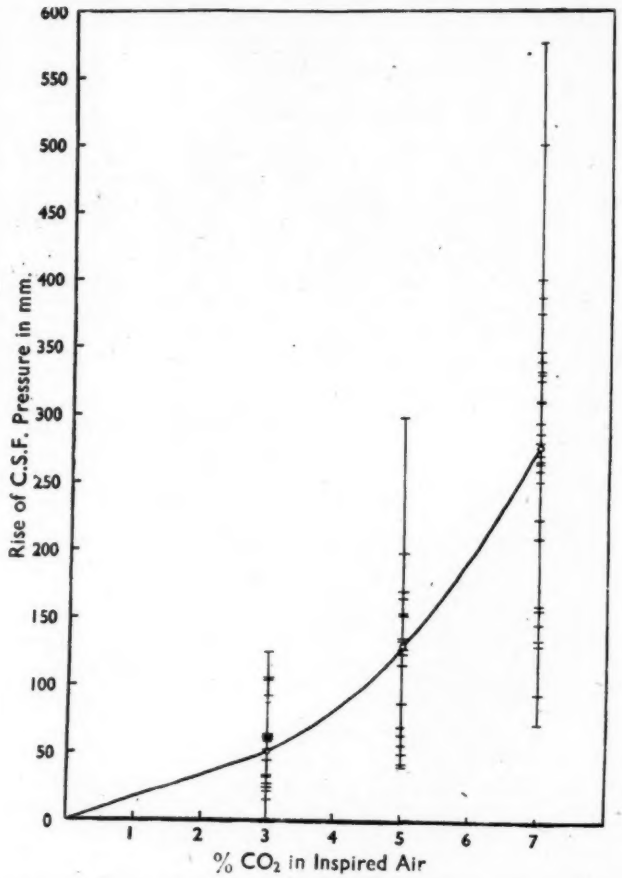

FIG. 2.—Increase in C.S.F. pressure breathing 3, 5, and 7% CO_2 in 29 emphysematous subjects.

and the respiratory response to the same concentration. For example, Case 1, whose ventilation increased by only 4 litres per minute with 7% CO_2, showed an increase of 500 mm. in C.S.F. pressure.

These observations demonstrate that both oxygen lack (low pO_2) and carbon dioxide excess (high pCO_2 and increased H-ion concentration) cause an increase in C.S.F. pressure, and the magnitude of their effect is enough to account for the considerable elevation in intracranial pressure observed in emphysematous subjects during respiratory infections.

Effect of Oxygen on the C.S.F. Pressure in Emphysema

In 10 experiments on normal subjects we have found that inhalation of pure oxygen for 10–15 minutes has no significant effect on the C.S.F. pressure. Davies and Mackinnon (1949) observed that inhalation of oxygen in cases of cor pulmonale with congestive failure caused an immediate and striking increase in C.S.F. pressure. Studies on Case 6 have confirmed their observation and provide an adequate explanation for this phenomenon.

This patient was admitted to hospital in October, 1950, with acute bronchitis. He had been dyspnoeic on exertion for four years and had suffered from severe throbbing headaches for the preceding 18 months. He was found to have advanced emphysema, cor pulmonale with early congestive failure, and bilateral papilloedema with retinal haemorrhages. The blood pressure was 160/100 and the maximum breathing capacity fluctuated between 16 and 30 litres a minute. On the second day after admission the C.S.F. pressure was 270–300 mm. and on the 18th day 420–440 mm. On the 27th day, when the signs of congestive failure had disappeared, the basal C.S.F. pressure breathing air was 220–260 mm. (Fig. 3). The minute-volume of ventilation was 8.03 litres (rate 21 × tidal air 382 ml.), the arterial oxygen saturation 89%, and the plasma carbon dioxide content 83 vols.% (normal level 60 vols.). At the 30th minute pure oxygen was administered via a rubber mouth-tube, and over the next 30 minutes a dramatic rise in C.S.F. pressure occurred, reaching a peak of 670 mm. The respiratory minute volume recorded over the last 5 minutes of oxygen inhalation had fallen by 30% to 5.77 litres (rate 20 × tidal air 288 ml.), the plasma carbon dioxide content had increased by 9 vols. to 92 vols., and the oxygen saturation had risen to 100%. At this point the patient felt drowsy but did not complain of headache. When inhalation of oxygen was discontinued, C.S.F. pressure fell rapidly and the respiratory minute volume rose to its pre-inhalation level of 8.11 litres

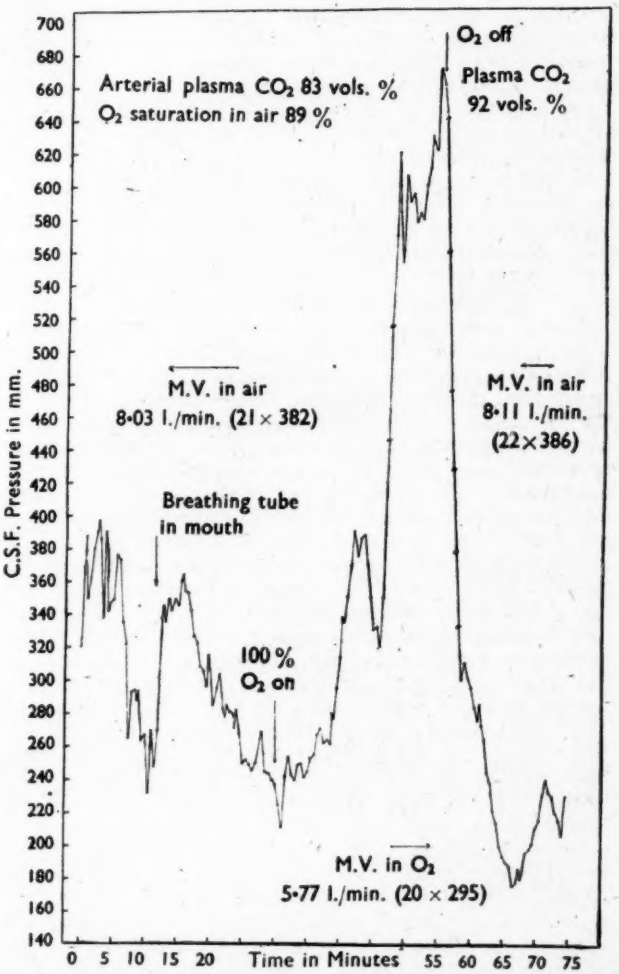
O2 off
Plasma CO2 92 vols. %
Arterial plasma CO2 83 vols. %
O2 saturation in air 89 %
M.V. in air 8·03 l./min. (21 × 382)
M.V. in air 8·11 l./min. (22 × 386)
Breathing tube in mouth
100 % O2 on
M.V. in O2 5·77 l./min. (20 × 295)
C.S.F. Pressure in mm.
Time in Minutes

FIG. 3.—Influence of inhalation of oxygen on the C.S.F. pressure, pulmonary ventilation, and arterial CO_2 content in an emphysematous subject.

(22 × 368). Subsequently papilloedema subsided completely without residual visual impairment. The patient was still alive in July, 1953, and, although completely disabled by dyspnoea on exertion, no longer suffered from headaches and the C.S.F. pressure was normal.

Discussion

Anoxia and hypercapnia might increase C.S.F. pressure by any of the following mechanisms: (1) increase in volume of C.S.F. due to more rapid formation or slower absorption; (2) increase in brain volume due to cerebral oedema; (3) increase in intracranial blood volume due to cerebral vaso-

dilatation; or any combination of the three. If the rate of C.S.F. formation was increased during the period of gas inhalation it would be expected that the pressure would remain elevated on discontinuing the gas mixture until absorption of the excess had restored normal volume and pressure. In fact, the pressure falls extremely rapidly—usually to 10–50 mm. below the pre-inhalation value (see Fig. 1). Raised venous pressure is thought to slow the rate of C.S.F. reabsorption via the arachnoid villae, and is the presumed cause of intracranial hypertension in congestive failure due to rheumatic heart disease. Inhalation of carbon dioxide does not, however, cause any significant change in venous pressure (Goldensohn *et al.*, 1951). This leaves mechanisms 2 and 3 as possibilities.

Wolff and Lennox (1930), by direct observation of the diameter of the pial blood vessels and measurement of the cisternal C.S.F. pressure in the cat, showed that inhalation of high carbon dioxide and high carbon dioxide plus low oxygen mixtures caused immediate vasodilatation with rise in C.S.F. pressure. Anoxia alone caused cerebral vasodilatation, but this effect was often offset by hyperventilation causing a fall of blood pCO_2. White *et al.* (1942) made quantitative studies on changes in brain volume, cerebral blood volume, and C.S.F. volume in cats. With low oxygen inhalation, brain volume increased considerably, but the cerebral blood volume remained unchanged. This was attributed to the effect of anoxia in causing cerebral oedema by increasing the permeability of cerebral vessels. When carbon dioxide was added to the low oxygen mixture vascular dilatation with increase in cerebral blood volume occurred, but there was no further increase in brain volume. The effect of hypercapnia alone was not studied.

Thus it seems probable that raised intracranial pressure in emphysematous subjects with acute respiratory infections is due to the combined cerebral vasodilator action of anoxia and carbon dioxide retention. The antagonistic effect of low pO_2 and low pCO_2 may explain why the C.S.F. pressure in Case 8 was within normal limits—the vasodilator effect of moderate anoxaemia (O_2 saturation 69%) being offset by the lowered level of plasma carbon dioxide (7 vols. lower than the patient's normal level). The rise of C.S.F. pressure breathing oxygen in Case 6 may be explained as follows: in this patient resting ventilation was largely maintained by the stimulus of anoxia—as is shown by the fact that ventilation decreased by 30% on breathing oxygen. Although relief of anoxia *per se* would tend to produce cerebral vasoconstriction and a *fall* in C.S.F. pressure, this was more than counterbalanced by the increase in blood carbon dioxide content resulting from the fall in pulmonary ventilation. The net effect was a further increase of cerebral vasodilatation and rise in C.S.F. pressure. On breathing air once more ventilation increased, retained carbon dioxide was washed out, and C.S.F. pressure fell to its original (though raised) level.

An increase in blood carbon dioxide content invariably occurs during oxygen therapy in emphysematous subjects (Westlake, 1953) and accounts for the fact that the C.S.F. pressure often remains elevated (cf. Cases 9, 10, and 11) despite relief of anoxia. It is only on full recovery from the acute respiratory infection—when normal or near normal gas tensions are restored—that the C.S.F. pressure also falls to normal.

Is Raised Intracranial Pressure the Cause of Mental Disturbance During Oxygen Therapy?—Oxygen therapy in emphysematous subjects is often complicated by mental disturbance and neurological symptoms—acute mania, disorientation, profuse sweating, salivation, myoclonic twitching, stupor, and coma (Barach, 1937; Davies and Mackinnon, 1949; Comroe, Bahnson, and Coates, 1950; Westlake, 1953). These symptoms are often attributed to raised intracranial pressure, but careful analysis of the mechanism involved makes this view untenable. In cerebral tumour (or other space-occupying lesion) raised intracranial pressure causes drowsiness and coma by decreasing cerebral blood flow, with consequent cerebral anoxaemia. In the emphysematous subject the rise in C.S.F. pressure that occurs during oxygen therapy is due to increased cerebral blood volume from pial vasodilatation. Cerebral blood flow, far from being diminished, is greatly increased (Kety and Schmidt, 1948; Patterson *et al.*, 1952). In the absence of any evidence that raised intracranial pressure *per se* (when unaccompanied by reduced cerebral blood flow) has any deleterious action on the function of cerebral neurones, we prefer to regard mental symptoms as manifestations of the direct action of hypercapnia and acidaemia on the brain (carbon dioxide narcosis) and do not believe that lumbar puncture has any therapeutic value.

Summary

Raised intracranial pressure in emphysematous subjects suffering from respiratory infections is attributed to the vasodilator action of anoxia and hypercapnia on cerebral vessels. During oxygen therapy the C.S.F. pressure may remain raised (despite relief of anoxic vasodilatation) owing to further rise in blood carbon dioxide content. Mental disturbance accompanying oxygen therapy cannot be directly related to raised intracranial pressure.

We wish to thank Dr. T. Simpson for permission to study cases admitted under his care, and for his continued encouragement and advice.

REFERENCES

Barach, A. L. (1937). *N.Y. St. J. Med.*, **37**, 1095.
Comroe, J. H., Bahnson, E. R., and Coates, E. O. (1950). *J. Amer. med Ass.*, **143**, 1044.
Davies, C. E., and Mackinnon, J. (1949). *Lancet*, **2**, 883.
Goldensohn, E. S., *et al.* (1951). *Amer. J. Physiol.*, **165**, 334.
Friedfeld, L., and Fishberg, A. M. (1934). *J. clin. Invest.*, **13**, 495.
Kety, S. S., and Schmidt, C. F. (1948). Ibid., **27**, 484.
Patterson, J. L., *et al.* (1952). *Amer. J. Med.*, **12**, 382.
Pickering, G. W. (1934). *Clin. Sci.*, **1**, 397.
Simpson, T (1948). *British Medical Journal*, **2**, 639.
Westlake, E. K. (1953). Disordered Respiratory Function and Carbon Dioxide Narcosis in Emphysema. M.D. Thesis. Cambridge.
White, J. C., *et al.* (1942). *Arch. Surg., Chicago*, **44**, 1.
Wolff, H. G., and Lennox, W. G. (1930). *Arch. Neurol. Psychiat., Chicago*, **23**, 1097.

EARLY TREATMENT OF CLEFT-LIP AND CLEFT-PALATE

BY

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The effective closure of congenital clefts of the lip and palate has presented a challenge which has been taken up by most of the great surgeons of the past century, and considerable ingenuity and daring have been evoked. Many lips and palates were closed without anaesthesia of any kind. To-day, with the help of anaesthesia, electric lighting, suction, and fine instruments and sutures, the surgeon works under improved conditions. Fewer babies with this deformity die than formerly, and actual closure of the clefts can be achieved with certainty. Fairly general agreement has been reached in this country on what procedures are desirable, but there is uneasiness concerning their shortcomings. Any surgeon who operates on these conditions realizes that some of his cases do not turn out as well as he would like. He knows that some will improve with the passage of time, but he will also have the fear that some may become worse. Little is known of the effects of operation on the development of the facial skeleton, and these may be serious enough to prohibit procedures otherwise commendable. Investigation along these lines requires the construction in each case, and with unoperated controls, of a series of models of the dental arches covering the period of growth, and no such survey is likely to be available for a number of years.

Bearing the above in mind, and also the inadequacy of any classification based on personal appraisal of cases, it has nevertheless seemed worth while to attempt to assess the effectiveness of treatment in a series of 100 consecutive patients with cleft-lip and/or cleft-palate admitted to Rooksdown House, the plastic surgery unit for the eastern area of the South-western Metropolitan Hospital Region.

Causation

As long ago as 1757 Trew mentioned heredity as a factor in the formation of congenital clefts, and since then many writers have pointed out the frequency of a family history of the condition: Muller (1886) and Haug gave 12%, Birkenfeld (1927) 20%, and Hinrichsen (1935) 24%. In 85 cases of the present series the parents had a reasonable knowledge of the child's forebears, and in 16 (18.8%) there was someone in the family with a cleft. Affected relatives were equally divided between the fathers' and mothers' families; they included the father's brother, sister, uncle, and great-aunt, and the mother's brother, uncle, great-uncle, and great-aunt. Few of us know much about our families two generations back, and the true figure would be greater than that given. From an examination of 703 family histories in cleft cases occurring in Denmark, Fogh-Andersen (1942) concluded that there was no genetic connexion between isolated cleft-palate and cleft-lip with or without cleft-palate. The positive family histories obtained in our series support this view.

Little is known of the manner of formation of clefts of the lip and palate, but they lie in the line of approximation of the nasal and maxillary processes and are presumably the result of failure in development and fusion of the mesoderm of these parts. Normally this fusion is first seen in the region of the nostril floor, and thereafter successively in the upper and lower portions of the lip. A little later union spreads through the hard and soft parts of the palate to the uvula. Failure to join may be complete, in which case a cleft extends through lip, alveolus, and palate; or incomplete, only part of the line of fusion being open. The nostril floor is the part least often cleft, and partial lesions extend towards this site from the lip border or from the uvula.

Table I shows that in 51 cases the cleft extended through the lip and palate, though in several there were small skin bridges in the region of the nostril and in 10 the alveolus was intact. In 36 the cleft was confined to the palate, and in 13 the lip was cleft and the palate intact, though in 4 of these 13 the alveolus was cleft.

TABLE I.—*Extent of Clefts and Sex Incidence*

	No.	Male	Female
Cleft lip and palate ..	51	38 (41·1%)	13 (16·4%)
Cleft-palates ..	36	20 (6·9%)	16 (13·6%)
„ lips	13	8 (14·4%)	5 (7·6%)
	Total	66 (62·4%)	34 (37·6%)

Figures in parentheses are, for comparison, from Fogh-Andersen's analysis of 703 patients.

The preponderance of the condition in males has been mentioned by numerous writers. Fogh-Andersen remarked on the greater incidence of cleft-palate in girls, among whom in his series it was twice as common as in boys, but in the present series the incidence was greater in boys (5:4).

Table II shows that clefts on the left side of the lip greatly outnumber those on the right and double clefts; this fact has been noted by many observers.

TABLE II.—*64 Cases of Cleft-lip: Extent*

	Lip Only	Complete Cleft	Lip and Palate
Left	10	22	7
Right	2	8	2
Double	1	11	1
Total ..	13	41	10

Associated Abnormalities.—Six children had associated abnormalities (Table III). It will be noted that none of these were situated in the extremities, although in the past these have been noted as the sites of most frequent allied anomalies (v. Verschuer, 1938). Fogh-Andersen estimates the incidence of such anomalies as 10%. This would be in approximate accordance with our figure, which takes no account of neonatal deaths or abnormalities becoming manifest later in life.

TABLE III.—*Associated Abnormalities*

Mental deficiency, ...	2
„ „ nystagmus, and optic atrophy ..	1
Hydrocephalus	1
Otitis media	1
Blindness; right eye absent, left cornea opaque ..	1

Treatment of Cleft-lip

With a large lip a good operative result is more readily obtained, but, in view of the unsightliness of the deformity, delay to allow growth of the parts is unwarranted, and the majority of these babies were operated on between the third and sixth months of life. One complete cleft was closed on the day of birth, and a partial lesion was treated for the first time at the age of 23 years. By the third month the parts have grown sufficiently for the surgeon to be able to make a shapely lip and nostril, and the child has a good enough hold on life to withstand the anaesthetic and the operative hazards.

On the whole, the general health of the children on arrival at hospital has been excellent. It seems now to be recognized that the existence of the widest cleft is no threat to life from the point of view of interfering with feeding or permitting nasopharyngeal infections, and no case has been referred for urgent closure for either of these reasons. Operation has occasionally been postponed because the child had a cold, or was underweight, or because the haemoglobin level was low (under 10.5 g.%), but in no case has operation proved impossible or injudicious. In 15 cases palate closure was carried out when haemolytic streptococci had been grown from the throat swab, and in none were there complications. No transfusions have been given, before or after operation, and in only one case, with post-operative gastro-enteritis, was intravenous fluid required. The absence of any mortality is explainable partly by insistence on absolute fitness for operation and partly by the care given by experienced anaesthetists and nurses.

In treating single cleft of the lip there are two methods of approach. The first is simply to pare the cleft edges at the primary operation, joining the lip in layers with minimal tension so as to spare the maxillary arches from pressure where the cleft is complete. This postulates the necessity for a scar excision in all layers at a later date, when the construction of a lip of normal shape will be facilitated by the growth which has taken place in the interim.

The second method is to attempt at the outset to make the lip and nose perfect. In the minute lip of the infant this is not easy, and any mistakes will be magnified by growth. On the other hand, the scar obtained early in life, even when the gap is wide, can be less noticeable than any made subsequently.

This series includes 10 cases of single cleft which had been closed on the former principle at other hospitals, and a further 17 children were treated similarly at Rooksdown House. With varying success, the attempt was made in most of these to adjust the nostril floor and alar base at the first operation.

In 22 others an attempt was made to perfect the lip and nose at the initial operation. Since the deficiency of lip tissue is most marked towards the margin, no simple paring of the cleft can produce a lip which pouts like that of a normal child, and it is necessary to cut into the lip and design complementary flaps. The Barrett Brown (Brown and McDowell, 1945) procedure was used in eight cases,

the Blair (Blair and Brown, 1930, 1931) in five, the Hagedorn in five, the Le Mesurier (1952) in three, and in one concavo-convex incisions as used by Vaughan and others. All of these cases, when reviewed, were found to have some fault which seemed worthy of surgical correction, and in this regard the primary operation failed in its objective. However, all such adjustments were minor, and there was no call to alter the original scars, which proved less obvious than those resulting from the two-stage method. A perfect result, though infinitely desirable, is not to be expected, and the tendency to seek perfection through a series of trimming procedures has been resisted. Even if the particular defect under consideration were corrected, each such operation takes something from the part and leaves it smaller. To quote Veau and Borel (1931), "Les petits détails de la lèvre qui souvent retiennent toute notre attention, n'ont pas la même importance que la forme générale du visage qui nous préoccupe moins."

Double clefts of the lip are usually associated with a serious deficiency of tissue, and their treatment presents the biggest problem in the field of lip and palate surgery. The method used in the 11 cases in this series was to close the lip in stages, first one side and a month later the other. The edges of each cleft were pared with care to preserve as much tissue as possible, closure being effected with three layers of sutures. In this way the soft tissues were draped in front of the prominent premaxilla, which was thereby subjected to a measure of tension and brought nearer alignment with the maxillae. While the appearance is improved by these operations, a number of secondary operations are needed, and a result comparable to that available in single clefts is extremely difficult to achieve.

Where a cleft is complete, closure of the anterior part of the palate at the time of lip closure is a convenience, since this region is relatively inaccessible later. With three exceptions this was attempted in the lip closures of this series; the exceptions were those done by the Le Mesurier technique, in which there was no time. In 23 the nasal mucosa was sutured with interrupted mattress sutures (Fig. 1, a). Dissection and suturing in this delicate layer is difficult, and closure was successful in only 14. In six cases the mucosa dissected from the nasal septum was sutured to the under aspect of the buccal mucoperiosteum raised at the cleft edge (Fig. 1, *b*), after the manner recommended by Dorrance (1933) for closing the hard palate. Closure was successful in four of these. This is easier than direct suture of the nasal mucosa, and the saving in time is important when there is so much to do.

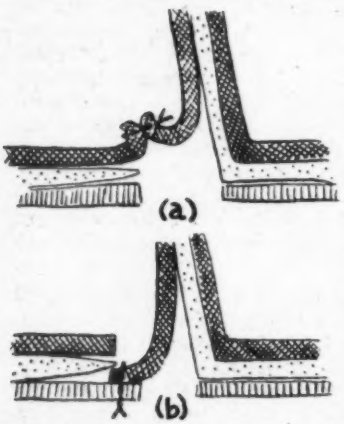

FIG. 1.—Alternative methods of closing the anterior palate.

Treatment of Cleft-palate

The primary reason for operating on the cleft-palate is to permit normal speech. The aim is to produce a palate which is long enough to be able to meet the posterior wall of the pharynx when in the elevated position and sufficiently mobile to achieve this with rapidity. Eighty-five operations were performed, six different techniques being used.

1. *Two-flap Method* (Fig. 2) (24 cases).—This resembles the original operation of Langenbeck (1861), but differs in that the nasal mucosa is not divided transversely. Closure is with two layers of sutures—one in the nasal mucosa, the other in the buccal mucoperiosteum. In the soft palate these buccal sutures approximate the muscles. Catgut was used in the first four; thereafter silk (2/0) was preferred because it seemed less irritating to the mucosa. These sutures do not require removal, since they come away by themselves.

2. *Three-flap Method* (Fig. 3) (33 cases).—This method differs from the above in that the mucoperiosteum is divided obliquely, a step which permits lengthening of the palate.

3. *Four-flap Method* (Fig. 4) (15 cases).—This is similar to the three-flap method, but employs two small flaps based in front for closure of the anterior part of a long cleft as described by Wardill (1933).

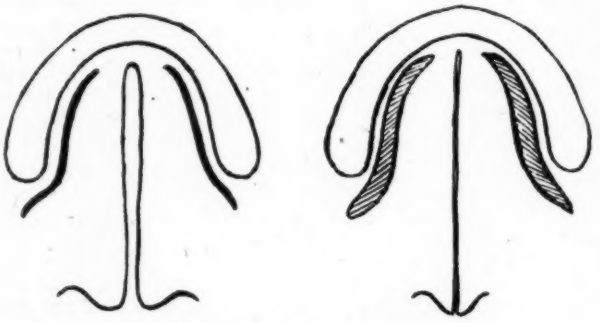

FIG. 2.—The two-flap operation.

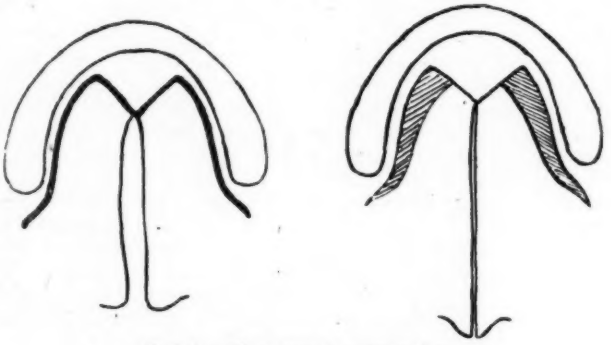

FIG. 3.—The three-flap operation.

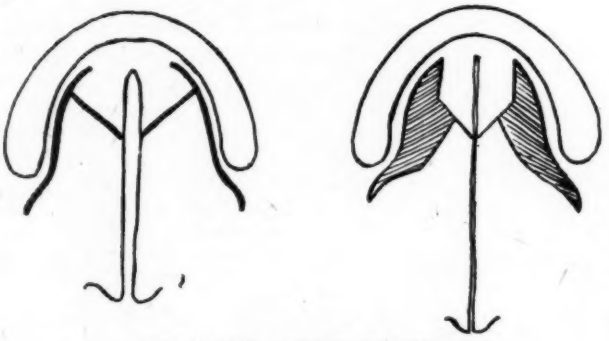

FIG. 4.—The four-flap operation.

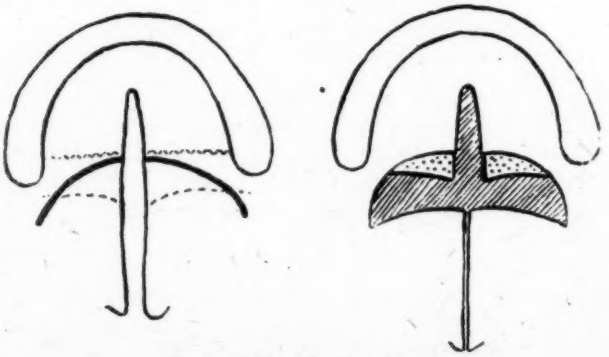

FIG. 5.—The X operation.

4. *X Operation* (Fig. 5) (11 cases).—Here the transverse division of the buccal mucoperiosteum is made further back, over the horizontal plates of the palate bones. As with the above operations, the nasal mucosa is not divided transversely, and is carefully sutured in the midline. This operation has only one advantage: it does not disturb the distribution of the greater palatine vessels and the blood supply of the transverse palatine suture, which may be a growth centre.

5. *Cuthbert (1951) Operation* (Fig. 6) (1 case).—Swinging across the left mucoperiosteal flap breaks the longitudinal suture line, which is an undesirable feature of the above procedures. To allow the flaps to move, the greater palatine vessels must be divided. Transverse section of the nasal mucosa opposite the posterior border of the hard palate favours increase in length.

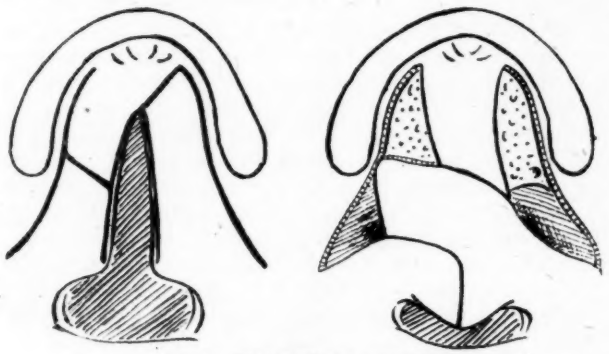

FIG. 6.—The Cuthbert operation.

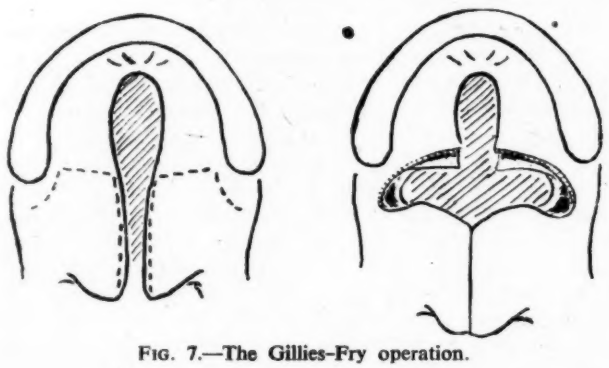

FIG. 7.—The Gillies-Fry operation.

6. *Gillies-Fry (1921) Operation* (Fig. 7) (1 case).—Here the soft palate is united after division of its elements from the hard palate. The latter, along with the aperture created behind it, is covered with an obturator.

In 39 cases, mostly early ones, the greater palatine vessels were divided at the point of emergence from the palatine foramina so as to permit easier approximation of the mucoperiosteal flaps. This step is rarely required, and preservation of the vessels must promote the viability of the flaps.

In 51 cases the pterygoid hamuli were fractured as recommended by Billroth. This permits prolapse of the tensor palati tendons and reduces transverse tension on the suture line. In the majority of cases in which early palate closure fails one of the tensor tendons is found in place and undisturbed, and its action would inevitably jeopardize closure. After fracture this bony process moves medially and dorsally under the influence of the fibres of the superior constrictor which are attached to it. There seems to be a danger that displacement of the hamuli may weaken the formation of Passavant's ridge, a fold of mucosa which forms on the posterior pharyngeal wall at the time of elevation of the palate. This ridge results from the contraction of a band of muscle fibres the majority of which are attached to the hamuli, and it is difficult to see how the muscle can contract effectively if both its bony attachments are mobile. The ridge is probably an important element in closing off the nasal from the buccal pharynx, as occurs constantly in speaking. In 34 cases, therefore, instead of fracturing the hamuli, tenotomy of the tensor tendons was performed.

Complications.—In two patients the operation failed, in that the entire soft palate broke down. One of these was a two-flap closure in which the hamuli had been fractured and the greater palatine vessels divided. In the other a four-flap closure had been done in conjunction with tenotomy of the tensors, the vessels being preserved. In neither case were haemolytic streptococci grown from the pre-operative throat swab, though in the second there was a staphylococcus. Fifteen cases, including 4 of the 11 X operations, developed small fistulae (Fig. 8) in the median suture line which required surgical closure. The 15 operations for obliteration of the fistulae were successful in all but two, and here the fistulae were close to the alveolus and therefore barely accessible.

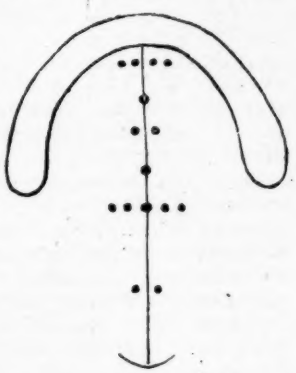

FIG. 8.—Location of post-operative fistulae. (All were in the midline.)

In two cases otitis media developed within a week of operation. In both the pre-operative haemoglobin levels were high (13.8 and 11.9 g.%), and in neither were streptococci grown from the throat swab. One occurred in November, the other in April, and both followed three-flap closures.

Results

Many difficulties arise in attempting to interpret speech results, and in this series there is the further obstacle that many of these children are very young and have a lot yet to learn about speaking. In 15 cases no estimate of the result is possible, and for the other 70 the figures given below are published in the realization that subsequent review may indicate inaccuracies.

Speech has been classified as follows: class I, apparently faultless; class II, faults distinctly minor, so that no one has any difficulty in understanding even in moments of excitement; and class III, unsatisfactory.

The results for the various operations are given in Table IV, and, while there is little between them, the four-flap comes out best. It is interesting to note that of the 15 cases operated on for post-operative fistulae 5 developed first-class speech. The following previously published results are given for comparison.

TABLE IV.—*Speech Results*

	No. of Cases	Class I	Class II	Class III
Two-flap operation	22	46%	36%	18%
Three „ „ ..	25	48%	40%	12%
Four „ „ ..	12	50%	42%	8%
X operation ..	9	45%	33%	22%
All methods ..	68	47%	38%	15%

1 Gillies-Fry operation: speech improved.
1 Cuthbert operation: not yet speaking.

Ritchie (1937) (100 cases): in 42 the speech was excellent, in 43 good, in 14 fair, and in 1 bad.

Oldfield (1949) (183 cases): in 87 the speech was excellent, in 79 good, and in 17 bad.

Bentley and Watkins (1947) (90 cases): in 46 the speech was perfect, 26 had minor faults, in 15 the speech was imperfect, and 3 were imbeciles.

Table V was made with a view to elucidating the respective merits of fracture of the pterygoid hamulus and tenotomy of the tensor palati. The results favour the latter, and

TABLE V.—*Comparison of the Speech Results Following Fracture of the Pterygoid Hamulus With Those Following Tenotomy of the Tensor Palati*

Speech	Fracture	Tenotomy
Class I	16	15
„ II	18	9
„ III	10	—
	44	24

of 31 patients who achieved class I, 16 had had fracture and 15 tenotomy, although almost twice as many were treated by fracture.

There has been considerable discussion about the optimal age for operation, with little in the way of statistics to substantiate the various views expressed. Wardill (1933) advocated operation early, in the expectation that the provision of an intact mobile palate before speech was attempted would permit this to develop in the normal way. Dorrance (1933) operated regularly at the age of 3 or 4 years, and claimed that speech was as good as with the early operation.

The results analysed in Table VI suggest that children operated on before the age of 9 months have a much better chance of achieving normal speech than those treated later,

TABLE VI.—*Age at Which Palate was Closed*

Age	No. of Cases	
6 to 9 months ..	16 ..	Class I speech in 77%
10 „ 12 „ ..	17 ..	„ „ „ „ 54%
13 „ 15 „ ..	18 ..	„ „ „ „ 53%
16 „ 18 „ ..	12 ..	„ „ „ „ 22%
19 „ 24 „ ..	7 ..	„ „ „ „ 2 cases
2 years	5 ..	„ „ „ „ 2 cases
3–4 „	3	
5 to 10 years ..	3	
11 „ 15 „ ..	1	
Over 15 „ ..	3	

and it should also be noted that no case operated on after the age of 3 years had a class I result.

Summary

In 100 cases of cleft-lip and/or cleft-palate both lip and palate were affected in 51, the palate alone in 36, and the lip alone in 13.

All lesions were more common in males.

In 18.8% there was known to be a relative of the child with a cleft.

Six children had associated congenital abnormalities, but in none was operation impossible.

Sixty-one operations were performed for primary lip closure and 85 for palate closure. There was no mortality.

Of the children born with cleft-palate, 47% are speaking without detectable abnormality, and a further 38% have only minor faults. Of the patients operated on under the age of 9 months, 77% speak normally.

REFERENCES

Bentley, F. H., and Watkins, I. (1947). *Lancet*, 2, 862.
Birkenfeld, W. (1927). *Bruns' Beitr. klin. Chir.*, 141, 257.
Blair, V. P., and Brown, J. B. (1930). *Surg. Gynec. Obstet.*, 51, 81.
—— —— (1931). Ibid., 53, 797.
Brown, J. B., and McDowell, F. (1945). Ibid., 80, 12.
Cuthbert, J. (1951). *Brit. J. plast. Surg.*, 4, 185.
Dorrance, G. M. (1933). *The Operative Story of Cleft Palate*. Saunders, Philadelphia.
Fogh-Andersen, P. (1942). *Inheritance of Harelip and Cleft Palate*. Arnold Busck, Copenhagen.
Gillies, H. D., and Fry, W. K. (1921). *British Medical Journal*, 1, 335.
Hinrichsen, R. W. (1935). *Zur Hasenschartenvererbung*. Kiel.
Holdsworth, W. G. (1951). *Cleft Lip and Palate*. Heinemann, London.
v. Langenbeck, B. (1861). *Dtsch. Klin.*, 13, 231.
Le Mesurier, A. B. (1952). *Surg. Gynec. Obstet.*, 95, 17.
Muller, E. (1886). *Bruns' Beitr. klin. Chir.*, 2, 220.
Oldfield, M. C. (1949). *Brit. J. Surg.*, 37, 178.
Ritchie, W. P. (1937). *Arch. Surg., Chicago*, 35, 548.
Veau, V., and Borel, S. (1931). *Division Palatine*. Masson, Paris.
v. Verschuer, O. (1938). *Erbarzt*, 5, 57.
Wardill, W. E. M. (1933). *Brit. J. Surg.*, 21, 347.

PERSISTENT ADULT BED-WETTING TREATED BY SACRAL NEUROTOMY

BY

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Definition and Aetiology

When the wide and varying group of cases loosely termed enuresis has been analysed and from it excluded all instances of precipitancy, defective control, and unintended bladder evacuation, diurnal or nocturnal, in which organic disease of the urinary tract (infections, developmental abnormalities of bladder and urethra) or of the nervous system has been demonstrated, there remains the clearly defined essential enuresis. This is a continuation of the irregular bladder action of infancy, commoner in the male than in the female, tending in most cases to be outgrown before puberty, though persisting in some cases until much later. It consists in bladder evacuation during sleep without awakening; in a great many cases there is an accompanying diurnal precipitate micturition amounting almost to incontinence and almost a strangury when it is attempted to hold back the urine. When in severe cases the enuresis finally ceases by degrees—as a rule with sporadic recurrences—the patient is left with a "weak" bladder with lifelong diurnal precipitate action.

During the years of active and frequent enuresis the life of the young patient is miserable; to go away from home is a recurring terror and shame, particularly as the most recent attitude appears to be that enuresis is a form of juvenile delinquency to be treated by "pep" talks and putting the young patient "on his honour"—the implications of which he greatly resents if he is at all sensitive and intelligent. Psychiatric thought regards it as an Oedipus matter—the boy, right on to adult life sometimes, wetting his bed to spite his mother and father for sleeping together. It is to the good that the time-honoured hunt for exciting causes (phimosis, worms, enlarged tonsils, etc.) has been abandoned, likewise the consequent operations, even as cures by suggestion. It is true that the patient can be "trained" to endure an uncomfortable bladder during the day for fairly long periods. This, however, is no more curative of the underlying condition than is inducing nocturnal anuria by fluid abstention during the latter part of the day. The exceptionally good results claimed on hospitalization, when the patient is wakened every hour or so during the night, are open to similar criticism. Treatment by belladonna (as a parasympathetic inhibitor) and by amphetamine (partly a mild sympathetic stimulant, but acting mainly by producing light if any sleep) have equally transient effects.

The unsatisfactory position of treatment is reflected in the enormous literature by the vagueness of views expressed regarding the underlying cause. In the agreed absence of identifiable organic disease, recourse is had to mental and psychiatric defects, reflex factors, and so on; the most positive view was the old expression "pelvic neurosis." It is interesting to note that some fifty years ago Cathelin practised the flooding of pelvic nerves with saline or anaesthetic solutions by epidural injection into the sacral hiatus for the treatment of

"pelvic neuralgias, sexual neuroses, and incontinence." Development of the view that the condition is an inborn defect of nerve control of the bladder has been greatly hindered by the even now highly controversial opinions on the mechanism of the latter.

Innervation of the Bladder

Even here, though the source, deployment, and final distribution of the vesical and other visceral pelvic nerves are well known, the matter is further complicated by a variable and inconstant nomenclature.

The bladder, seminal vesicles, prostate, and lower ends of the ureters, among other organs, are supplied by numerous filaments of the (inferior) hypogastric plexus, which lies in the lateral part of the true pelvis. The part of it supplying the bladder is sometimes termed the extrinsic vesicle plexus; it is without any sharp demarcation from the rest of the plexus, however. In the submucous and muscular coats fine intrinsic (vesical, urethral, etc.) plexuses are formed before the final distribution of fibres. On both the intrinsic and the extrinsic plexuses the fibres subserving opposing functions are indistinguishably mixed; no satisfactory inferences may be derived from disease in, or stimulation of, either of these situations.

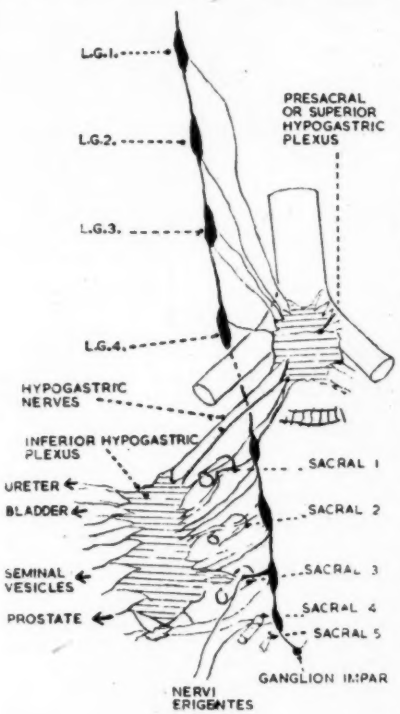

FIG. 1

Sources of Bladder Innervation.—The (inferior) hypogastric plexus is formed from: (*a*) *The lumbar sympathetic.* Branches from the lumbar ganglia pass to the presacral or superior hypogastric plexus; the innervation ultimately reaching the bladder is derived probably from the first and second ganglia. From the presacral plexus the fibres pass to the (inferior) hypogastric plexus via the hypogastric nerves, some possibly via branches to the pelvic parasympathetic chain. The site of synapse is open to dispute, but does not affect the question of function. (*b*) *The sacral nerves.* Filaments pass from the trunks of S 2, 3, and 4 immediately on their emergence from the sacral foramina; the major contributor is usually S 3, the least S 4. Some of the fibres pass direct to the hypogastric plexus, others to the ganglia of the pelvic parasympathetic chain—a continuation of the lumbar chain passing under the common iliac vessels—to lie immediately in front of the sacrum slightly medial to the foramina. The sacral branches—short filaments 4–8 mm. long—pass, therefore, some slightly medially, to join the parasympathetic chain and others laterally to join the plexus. They are best displayed by lifting the cord forwards and outwards. The parasympathetic chain gives numerous branches throughout to the plexus.

Function

(*a*) *Motor.*—Since the classic researches of Learmonth there has been little or no doubt concerning the main function of the sympathetic component: stimulation causes contraction of the bladder neck of the prostatic and seminal vesicular musculature, and of the ureteral orifices, together with relaxation of the detrusor. This part of the innervation is capable of simulation (hypogastric nerves, presacral plexus) without overflow of stimulus into the sacral part; but a brief consideration of the anatomy shows that the effects of pure stimulation of the latter are practically impossible to obtain. That the function of sacral innervation is antagonistic to the sympathetic is inherent in the term parasympathetic: the nomenclature which applies this term to the cord continuing the lumbar sympathetic into the pelvis is unfortunate and misleading. The evidence comes from several sources: compression of sacral nerves by very low spinal disease; operative removal of parasympathetic trunks; and disease or operative damage—for instance, in abdomino-perineal resection of the rectum with a posteriorly adherent growth—all show that damage or removal of the sacral supply leaves a bladder now solely under sympathetic control, without emptying power, and with an obstinately contracted neck. This confirms the quoted effects of sympathetic stimulation and disproves the view that the sacral supply controls both emptying and retention.

(*b*) *Sensory.*—The question of sensation is more under dispute, and in particular whether the sympathetic supply is sensory in addition to motor. Several observations favour such a view. For instance, patients with a transverse cord lesion above the sacral level "have been aware of filling and emptying of the bladder"—the cautious and honest wording is to be noted. Stimulation of the presacral nerve in the conscious patient has caused an accurately localized pain over the bladder. On the other hand, presacral neurectomy gives very little relief of chronic bladder pain. The vesical sensation in cord lesions may well be peritoneal in origin. I incline to the view that it is vasomotor in origin, adducing my experiences with local analgesia of the bladder.

Local Analgesia of the Bladder

During the past 13 years I have performed some 700 prostatic and bladder-base operations under a local analgesic combination. The essential feature is sacral spinal anaesthesia. With the patient sitting, about 0.8 ml. of hyperbaric cinchocaine hydrochloride is injected without barbotage through the lowest interspinal interval, 12–15 minutes being allowed for fixation. The upper level of anaesthesia is S 1, shown by paraesthesia of the Turkish slipper area. On the table the hypogastric abdominal wall is anaesthetized by a fan of infiltration with 0.5% procaine*; for vasectomy a further small injection into the cord, supplied from D 12 to L 1, is required. The method was adopted in order to undertake prostatic operations in even the worst cardiovascular risks: it was developed from the knowledge that transurethral diathermy and resection can be painlessly performed under low spinal analgesia alone, always provided that S 1 shows clear signs of anaesthetization. Ordinary sensation—pain of cutting and burning, and, in the enucleation of adenomata, distension of the prostatic bed and the adjacent trigone—therefore travels purely via the sacral nerves.

It was originally intended that the sympathetic element, even in the lumbar region, should be unaffected, in order to avoid the least fall in blood pressure; it was not foreseen that the preservation of the sympathetic supply would result in a most helpful and favourable "fluke"—the removal of sacral inhibition giving virtually a sympathetic stimulation. After enucleation of adenomata the bladder base and prostatic musculature contract down, providing an active haemostasis lasting with cinchocaine some three hours. (This contrasts most favourably with the false haemostasis seen with high spinal analgesia, resulting often in severe reactionary haemorrhage.)

In cystoscopy it is observed that a low spinal analgesic is undesirable when it is necessary to catheterize ureters; the contraction of the bladder base, particularly of the

*Adrenaline should not be employed in elderly patients as there is a great risk of setting up fibrillation.

musculi ureterae, sharply angulates the intramural course of the ureter, making it impossible for the catheter to do more than just enter the orifice. Further, with sacral spinal anaesthesia there is retention as long as the anaesthesia lasts. These various experiences confirm—were it necessary—the retentive sympathetic control described by Learmonth; the effect is clearly not a *purely* vascular one as is sometimes held.

The Bladder-emptying Mechanism

There is evidence to support the view that two distinct types of sensory impulse derive from the bladder base—first, the discomfort and pain when distension begins to stretch the trigone, and, secondly, that of the prostatic urethra which is associated with the sensation of micturition (this is evoked clinically when the examining finger presses into the prostatic groove and in painful disease amounts to strangury). Physiologically, when urine enters and distends the prostatic urethra the sensory impulse via the sacral nerves sets off the detrusor-stimulating, sympathetic-inhibiting reflex of micturition, which then becomes automatic. The trigonal and the prostatic sensations are distinct and different; for long the increased frequency of "middle lobe" prostatic enlargement has been attributed to the carrying up into the bladder of this "trigger" prostatic mucosa and to its being subjected to urinary contact (better, participation in trigonal stretching).

Mechanism of Enuresis

An enticing explanation of the phenomena of enuresis would be an ectopic distribution of the innervation of the prostatic urethra, overlapping the bladder neck and extending on to the trigone: the upward growth of the prostate would engulf the ectopic area progressively, accounting anatomically for the amelioration in most cases, and particularly in some severe ones about puberty. Confirmation by *cystometry* is difficult to obtain, for observations made with a catheter in contact with the urethra clearly present fallacies, as would the use of any form of anaesthetization to remove the effects of stimulation by the instrument. The usual cystometric findings in enuresis are that distension of the bladder up to a considerable volume is tolerated normally, but then extreme intolerance, urgency, and precipitancy develop. There is therefore neither a mental basis nor a general trigonal hypersensitiveness, for the volume tolerated implies a considerable degree of trigonal stretching; the specific reaction occurs when the stretching affects the bladder neck, the last place to be affected by the process. In the enuretic this seems to behave as if innervated like the prostatic urethra.

The alternative hypothesis is "parasympatheticotonia"—both motor and sensory; the former implying excessive inhibition of the retentive factor, the latter sensory hypersensitiveness (that this does occur is shown by the occasional patient who is completely unable to permit even a soft catheter to remain in his urethra). The converse—sympatheticotonia—has been accepted as a cause of sphincter disturbances in, for instance, achalasia of the cardia and hydronephrosis, and it seems reasonable to extend the type of explanation to enuresis, in which it seems more satisfactory than the idea of an ectopic nerve supply. In either case, however, a surgical reduction of the nerve supply to the bladder base and prostatic urethra clearly offers itself as a radical, or at least a *permanent* symptomatic, treatment of enuresis.

Sacral Neurotomy

There being no information whether the sacral supply has a segmental character—for example, does S 2 supply the trigone and S 3 the prostatic urethra?—as might be expected on developmental grounds, an empirical reduction in the nerve supply should increase sphincter tonus, decrease detrusor tonus and sensitivity, and produce a normal balance. Division of the fibres from S 2 on both sides and crushing of those from S 3 on one side is a likely compromise, interfering temporarily only with part of the components of nervi erigentes. In the typical case the scales swing strongly to the side of retention for several days, a balance between the two functions being recovered in ten days or so.

Operation

With the patient in a moderate Trendelenburg position, the abdomen is opened in the midline below the umbilicus and the gut packed conveniently away. The pelvic peritoneum is incised posteriorly from the midline at the sacral promontory down to the right of the rectovesical pouch (Fig. 2). The edges of the peritoneum are lifted gently aside along the whole extent and the presacral fascia is similarly divided (Fig. 3). Neither procedure is attended with more than the slightest bleeding. The edges of the fascia, held by forceps, are very gently and gradually raised and peeled outward by gauze dissection on the right side; the parasympathetic chain and the sacral foramina come into view. The former is easily seen; the latter are obscured by loose connective tissue, fat, and small veins No attempt should be made to demonstrate them by dissection laterally to the parasympathetic chain until the latter has been elevated and drawn outwards; their branches are then seen, some going to the chain and some direct to the hypogastric plexus (Fig. 4). The temptation to define the foramina other than by touch must be resisted, for any dissection is almost certain to result in haemorrhage from fragile veins obscuring and staining the fine filaments and rendering accurate section uncertain. With the chain well raised and drawn outwards, the branches from S 2 and S 3 can be fully defined by gentle open-and-shut forceps-tip movements. All branches from S 2, both to the chain and outwards to the plexus, are divided, and the foramen is covered with a small disk of wax. The branches from S 3 are crushed. The exposure is repeated on the left side, and branches of S 2 are divided and a disk of wax, in later cases a small sheet of aluminium foil, again is applied over the foramen. The presacral fascia, the peritoneum, and the abdominal wall are closed in the normal appropriate way.

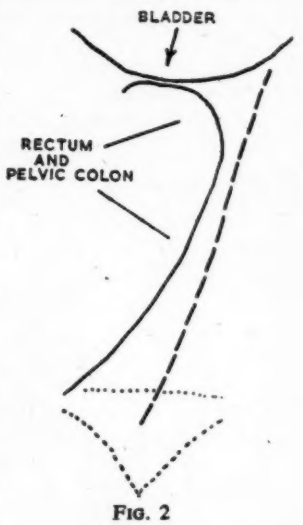

FIG. 2

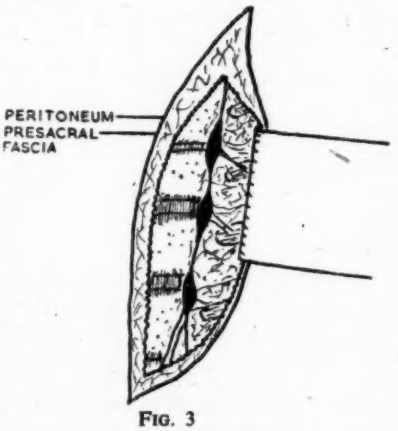

FIG. 3

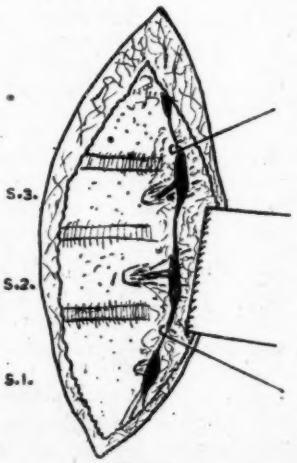

FIG. 4

Case Reports

Case 1.—A man aged 23, admitted for interval appendicectomy; enuresis since infancy, also diurnal urgency; had to rush to leave class at school. Treated by medicines and tablets (amphetamine recently), fluid restriction in latter part of day, micturition very late at night, etc. Had given up all treatment as a bad job. Enuresis about four to six times a week; even in hospital, with very restricted fluid, enuresis occurred two nights in four when awaiting operation. No organic disease of nervous or urinary system. Cystometry; 4 oz. (113 ml.), pressure 16 cm.; 10 oz. (283 ml.), 18 cm.; 16 oz. (454 ml.), 21 cm.; 17 oz. (480 ml.), precipitate emptying of bladder. Admitted for interval appendicectomy, he gladly accepted the chance that a nerve section might at least improve his condition. At operation S 2 divided on both sides; S 3 crushed on the right. Appendicectomy. In this first case the procedure, above recommended, of elevating and drawing outwards the chains was not adopted, and the foramina were exposed and defined by blunt dissection. Exceedingly troublesome bleeding made accurate nerve section difficult and problematic. During convalescence he had complete retention for first 24 hours, and passed a great deal at a time; during the next eight days frequency gradually returned to normal. The urgency by day disappeared. He reported at intervals after discharge; enuresis recurred, but to a far less extent than before—twice a month, three times a month, even five or six times a month. This was without precautions about taking of fluid, getting up last thing at night, etc. The daily urgency has completely disappeared. This is the state at 28 months after operation; clearly only a partial success owing to the uncertainty in the operative procedure, and to regeneration.

Case 2.—Male aged 20; enuresis since infancy, treated with numerous drugs and tablets and restricted fluids with temporary and slight improvement, but always relapsing on cessation of treatment to nightly bed-wetting even with restricted fluid and late waking; enuresis in hospital five times a week (admitted for operation on tendo Achillis). No gross organic disease in nervous or urinary system. Cystometry: 4 oz. (113 ml.), pressure 14 cm.; 8 oz. (226 ml.), 16 cm.; 12 oz. (340 ml.), 21 cm.; 16 oz. (454 ml.), 21 cm.; 18 oz. (510 ml.), precipitate emptying of bladder. Sacral parasympathotomy performed; branches S 2 divided both sides; S 3 crushed on right. During three weeks' convalescence in hospital no enuresis, though none of previous precautions taken. During first four days large quantities passed at wide intervals; micturition, initiated only when bladder contained as much as 18 oz. (510 ml.), was easily controlled and quite effortless. Thirteen months later he reported enuresis now thrice a week since operation. No precautions had been observed; the diurnal urgency had completely disappeared; there was no abnormality of bladder or of sex function.

Case 3.—Female aged 23. Enuresis at least three times a week; daily frequency four or five times, always with great precipitancy. Unaffected by dexamphetamine sulphate or fluid intake. Cystometry: pressure 70 cm., volume 700 ml., intense and precipitate micturition (continuous flow); 40 cm. pressure, intense desire to micturate (interrupted flow). No organic disease of urinary or nervous systems. Operative division branches S 2 both sides, crushing S 3 on right. Post-operatively no precautions taken; during 18 days' convalescence she always woke at night when micturition was needed; had never done this in her life before. Reporting nine months later, stated bed wet thrice in each month without any precautions taken.

Case 4.—Male 22. Enuresis since childhood, now five or six times a week, great diurnal precipitancy. Had had treatment by medicines and tablets, restricted fluid, waking by alarm clock in early morning, etc. No organic disease of urinary or nervous systems. Cystometry: 5 oz. (142 ml.), 14 cm. pressure; 10 oz. (284 ml.), 16 cm.; 15 oz. (425 ml.), 20 cm.; 17 oz. (480 ml.), precipitate emptying. Sacral parasympathotomy; S 2 divided both sides, S 3 crushed on right; fine filaments from S 1 on both sides also divided. Normal post-operative course. No enuresis in 16 days; diurnal precipitancy gone. Reported ten months later: no enuresis since discharge, though no precautions taken; still free from diurnal precipitancy.

Case 5.—Male 23. Enuresis six nights in seven. All the usual remedies have been tried. Great daily frequency with precipitancy. Cystometry: 5 oz. (142 ml.), pressure 15 cm.; 10 oz. (284 ml.), 16 cm.; 15 oz. (425 ml.), 20 cm.; 16 oz. (454 ml.), precipitate emptying. *This was repeated after administration of a sacral spinal anaesthetic;* similar pressures were recorded, but with 20 and 25 oz. (568 and 710 ml.) there were *pressures of 24 and 27 cm. still without emptying.* Sacral filaments from second divided on the right, from third on both sides; aluminium foil applied over the roots. There was complete retention for 30 hours relieved by catheterization; at the end of a week micturition occurred about every five hours. At the end of five months no recurrence of enuresis; precipitancy of micturition also had not recurred.

Comments

Whether the view taken of the essential nature of enuresis is correct or not, the cases treated by nerve section show one very partial cure over 26 months, no doubt owing to insufficient nerve division and regeneration, two very near cures of 14 and 16 months, and one nine-months cure. In all cases none of the previous restrictions and precautions have been observed; in all, the previous precipitancy had disappeared. The choice of nerve fibres for section is admittedly empirical; it would appear, however, that in the later cases a middle course has been successfully steered between the Charybdis of enuresis (an exaggeration but not entirely inapt !) and the Scylla of retention; the use of crushing only of S 3 was resorted to in case there was, so to speak, over-correction of the enuresis, when nerve recovery would correct this error. On the whole, the amount of nerve division is, if anything, on the timid side. Many more precautions are needed against regeneration. Any mention of an operation on the pelvic sympathetic seems automatically to evoke great concern for the nervi erigentes. There has been no complaint on this score, and, in any case, only a small part of their origin is put temporarily out of action. It might be argued that a temporary damping down of the function concerned in the adolescent male would not be entirely a bad thing.

The cases operated on have been of the severest type; it remains to be seen if the parents of a lad of 10 years or so, with nightly enuresis and the probability of years more of the humiliating condition before a problematic recovery ensues, will not seriously consider the prospect of cure afforded by an operation of little more than interval appendicectomy risk and inconvenience.

The application and extension of the procedure to other conditions is no part of the present communication; it is clearly a necessary adjunct to complete interruption of the sympathetic supply to the pelvis in order to obtain complete denervation for painful conditions, and is simpler than the wide and not entirely satisfactory excisions of hypogastric plexuses that have been used. It should afford at least symptomatic relief in cases of stress incontinence, and even in some cases of inexplicable habitual abortion.

The work of the speech therapist, an occupation open to both men and women but so far followed mainly by women, is described in a booklet recently issued by the Central Youth Employment Executive (*The Speech Therapist.* Choice of Careers Series, No. 51, H.M.S.O., 6d.). Details are given of the work in school clinics, which deal solely with children, and in hospitals, where both children and adults are treated. Information is given on the educational qualifications required, arrangements for training, employment prospects, and salaries. This booklet is one of a series intended primarily for boys and girls who are about to decide the kind of work to take up on leaving school.

CLINICAL APPLICATION OF PORTAL VENOGRAPHY

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The differential diagnosis and the full clinical assessment of splenomegaly can even to-day be an interesting and at times puzzling task. Conditions are met with in which the aetiology and pathogenesis of an enlarged spleen remain unexplained in spite of exhaustive bedside study and radiological investigations.

Modern advances in vascular surgery alone make it desirable that there should be a clear recognition of those cases of splenomegaly in which some of the symptoms can be remedied by vascular anastomosis for relief of portal hypertension. Attempts to demonstrate the portal system by injection of radio-opaque substances into a branch of the coronary vein, into veins draining the caecum, into the main portal branch, and into the branches of the splenic vein were carried out in recent years (Blakemore and Lord, 1945; De Sousa Pereira *et al.*, 1949; Moore and Bridenbaugh, 1950; Santy and Marion, 1951). The techniques employed were difficult, and not without risk to the patient, and, of course, only possible after laparotomy.

Abeatici and Campi (1951) were the first to describe a method of percutaneous portal venography in a dog via the spleen and splenic vein, and Leger (1951) applied the same technique in man for the first time. Soon afterwards, Boulvin and co-workers (1951) described their technique of portal venography by the same route in great detail. Their first patient suffered from cirrhosis of the liver and the second from an extrinsic obstruction of the splenic vein. These authors pointed out the potential value of the method for the differentiation of intrahepatic and extrahepatic block. Dreyer and Budtz-Olsen (1952) applied splenic venography in 11 patients with palpable spleens and again suggested the clinical application of the method. Milnes Walker and co-workers (1952) were the first in this country to publish their findings of portal venography by intrasplenic injection on 12 occasions, again in patients with enlarged spleens. Of particular interest was their demonstration of the flow from the portal vein into the left inferior vena cava nine months after successful end-to-side anastomosis between the portal vein and the inferior vena cava.

Konar and Sen Gupta (1953) related their experiences of splenic venography in 14 cases, which included cases of portal hypertension and of splenomegaly of unknown cause.

Present Investigation

We have applied the method of percutaneous intrasplenic injection on over 50 occasions, using a similar technique to that described by Boulvin and co-workers. Good contrast was obtained with 50% diodone, and this strength was used in all but one patient, who received a 70% solution. In some patients several films were taken at three-second intervals, but in most cases we were satisfied with the result of a single exposure after an injection of 18 ml. of the solution. A fine flexible lumbar-puncture needle with short bevel was used. The needle was entered in the left posterior axillary line just below the tenth rib with the patient on his back, but we have also obtained satisfactory pictures by injection into the tenth intercostal space in the scapular line, with the patient lying face down. The technique in normal people with healthy spleens is naturally far more difficult than in cases of splenomegaly.

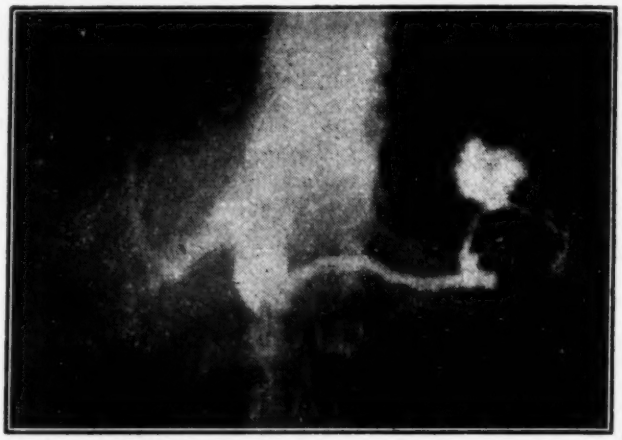

FIG. 1.—Unusual but not abnormal splenogram.

FIG. 2.—Splenogram in pernicious anaemia with splenomegaly.

Exact location of a healthy spleen by percussion was nearly always impossible, and we therefore had to rely on touch when the needle met resistance on entering the spleen. Several times we failed to hit the spleen and diodone was injected into the peritoneal cavity, and on at least one occasion into the splenic flexure of the colon. No ill effects followed. With growing experience we learned to appreciate the degree of resistance to the injection which is to be expected when the needle has pierced the spleen. We found the spleen a rather mobile organ, which may move about 2 in. (5 cm.) medially before the needle point enters the splenic capsule. In consequence the splenic vein appeared kinked, as shown in Fig. 1, which was the result of an injection into a healthy spleen through the scapular line. Tortuosity of the splenic veins was observed on several occasions in healthy people as well as variations in the size of the splenic and portal veins. In our experience no significant changes are to be expected after diodone injections into enlarged spleens without portal hypertension or extrahepatic obstruction. The dye did not spread to any extent within the spleen, and distinct filling of the splenic and portal veins and its intrahepatic branches was observed using no more than 12–18 ml. of diodone (Fig. 2). The intrahepatic distribution of the portal vein is shown up in a liver grossly enlarged due to melanoblastoma (Fig. 3).

Fig. 4 belongs to a series of eight splenograms taken in a patient with cirrhosis of the liver over a period of 14 months. The degree of portal hypertension as seen on portal venography varied in this patient, corresponding to changes in the clinical picture. A chronic hepatitis was originally confirmed by laparotomy, and his liver disease

was complicated by right lower lobe bronchiectasis. Each acute attack of bronchial suppuration was followed by deepening jaundice and increasing ascites, which improved under streptomycin treatment. We obtained normal splenograms in this patient when the ascites and jaundice subsided, but could demonstrate anastomoses with gastric veins of varying degree during acute exacerbations of hepatitis, of which Fig. 4 is one example. A severe degree of portal hypertension in another patient with appearances of oesophageal veins is demonstrated in Fig. 5. We were able to demonstrate a fine trickle of the dye through an almost completely thrombosed splenic vein in a young male patient with cirrhosis of the liver. The pathology was subsequently confirmed at operation. Fig. 6 was taken in a case of carcinoma of the stomach with secondary deposits in the portal fissure. The abrupt cessation of the flow of diodone along the splenic vein confirmed an extrahepatic block. Similar pictures were obtained in a patient with advanced carcinoma of the head of the pancreas.

Discussion

We have found intrasplenic portal venography a useful help in the diagnosis of splenomegaly of unknown origin, in the differentiation of intrahepatic and extrahepatic venous block, and in the assessment of the degree of portal hypertension and the anatomy of the anastomosis between the splenic vein and gastric and oesophageal vessels.

The technique presents no difficulties in cases with enlarged spleens, in contrast to injections into normal spleens, when failure to enter the splenic tissue on account of the mobility of the organ is frequently to be expected.

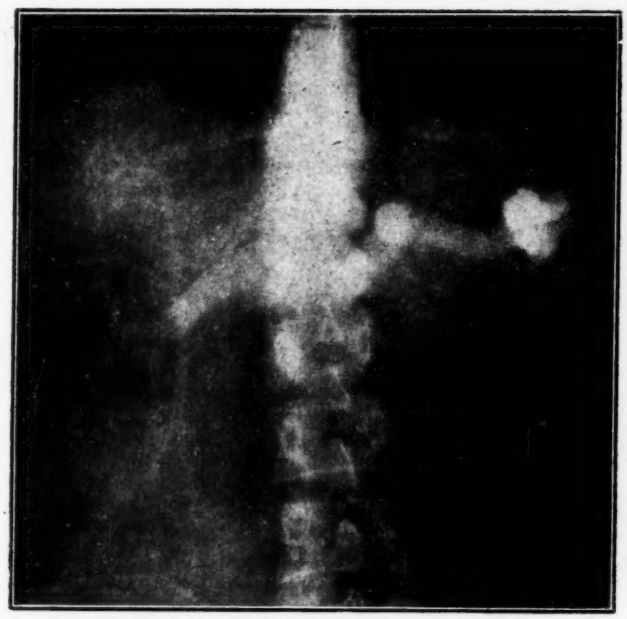

FIG. 3.—Melanoblastoma of liver.

FIG. 4.—Portal hypertension.

FIG. 5.—Severe degree of portal hypertension.

FIG. 6.—Carcinoma of stomach with secondary deposits in portal fissure.

We are indebted to Professor Charles Wells for permitting us to use the method on three of his patients who were about to undergo shunt operations.

REFERENCES

Abeatici, S., and Campi, L. (1951). *Minerva med., Torino*, **42**, 593.
Blakemore, A. H., and Lord, J. W., jun. (1945). *Ann. Surg.*, **122**, 476.
Boulvin, R., Chevalier, M., Gallus, P., and Nagel, M. (1951). *Acta chir. belg.*, **50**, 534.
De Sousa Pereira *et al.* (1949). Communication to the Academy of Sciences, Lisbon.
Dreyer, B., and Budtz-Olsen, O. E. (1952). *Lancet*, **1**, 530.
Konar, N. R., and Sen Gupta, A. N. (1953). *British Medical Journal*, **2**, 810.
Leger, L. (1951). *Mém. Acad. Chir., Paris*, **77**, 712.
Moore, G. E., and Bridenbaugh, R. B. (1950). *Surgery*, **28**, 827.
Santy, P., and Marion, P. (1951). *Presse méd.*, **59**, 221.
Walker, R. M., Middlemiss, J. H., and Nanson, E. M. (1952). *Brit. J. Surg.*, **40**, 392.

NEOMYCIN IN PYOGENIC SKIN DISEASES

BY

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Pyogenic infections are the commonest cause of skin disease, and cure of the acute case can be simple, but even impetigo, when mishandled, may persist for many weeks. Although the local use of antibiotics has considerably shortened the duration of these illnesses, it presents two disadvantages which some have thought contraindicate their use: (1) the danger of sensitizing the patient and thus preventing future systemic treatment with the antibiotic in what might be a serious illness; and (2) the encouragement of antibiotic-resistant organisms.

A stable and effective antibiotic which is not used systemically, which causes little cutaneous reaction, and which has a low incidence of bacterial resistance would overcome the most valid objections to local antibiotic therapy. Neomycin appears to fulfil these requirements in infections with *Staphylococcus pyogenes*.

Neomycin was discovered by Waksman and Lechevalier in 1949. It is produced by a strain of streptomycetes related to *Streptomyces fradiae*. It is water-soluble and thermostable, and maintains its effectiveness in practically any vehicle, including both acid and alkaline aqueous solutions. The drug is bactericidal *in vitro* against a wide variety of Gram-negative and Gram-positive organisms. Toxic effects causing kidney damage and deafness have prevented the parenteral administration of the drug, and its present use is limited to oral administration as an intestinal antiseptic and to local application. The effectiveness of neomycin as a local application in pyogenic skin eruptions has been reported in America (Kile *et al.*, 1950, 1952; Livingood *et al.*, 1952; Kimberly, 1952).

Present Investigation

A series of 93 cases were treated. They included: impetigo, 48; sycosis barbae, 18; ecthyma, 10; infected eczema and dermatitis, 8; furunculosis, 5; infective eczematoid dermatitis, 3; and blepharitis, 1. In none of these cases was irritation or sensitization of the skin caused by the ointment.

Neomycin was used in a concentration of 5 mg. per g. in an ointment base consisting of

White mineral oil	25%
Wool fat	20%
White petrolatum	54.4%

For purposes of comparison of bases, the same concentration was used in a water-miscible base:

Emulsifying wax, *B.P.*	20%
White petrolatum	20%
Phenoxyethanol	2%
Borax	0.6%
Boric acid crystals	1.2%
Water to	100%

The two bases were used on the impetigo cases, half the series being treated with the water-miscible base. In contrast to the experience of Forbes (1952), no appreciable difference in the clinical results was found.

The patients were instructed to apply the ointments three times daily, cleaning the affected areas and removing crusts with liquid paraffin. In the few cases of furunculosis treated the ointment was also applied once daily into the nostrils.

Bacteriology

The organisms were cultured from each case and their sensitivity to penicillin, streptomycin, chloramphenicol, aureomycin, and neomycin was estimated. From practical experience it was found that a *Staph. pyogenes* which was insensitive to less than 25 units of penicillin per ml. or to 50 μg. of chloramphenicol or aureomycin could be regarded as resistant to the respective drug as a local application.

Staph. pyogenes was found in 91 cases—46 were penicillin-resistant, 2 aureomycin-resistant, 18 chloramphenicol-resistant, and 1 was resistant to less than 16 μg. of neomycin. All other staphylococci were sensitive to less than 4 μg. of neomycin; in 70 cases the staphylococci were sensitive to less than 0.015 μg. of neomycin. A haemolytic streptococcus was found alone in two cases and in association with *Staph. pyogenes* in 20 cases. The only other organism isolated was *Pseudomonas pyocyanea* in one case of impetigo. This was resistant to penicillin, aureomycin, and chloramphenicol, but sensitive to streptomycin and neomycin.

In the 48 cases of impetigo a *Staph. pyogenes* was found alone in 37, a haemolytic streptococcus in association with *Staph. pyogenes* in 10, and a haemolytic streptococcus alone in 1. The staphylococci were resistant to penicillin in 34 cases and to chloramphenicol in 11.

The 10 cases of ecthyma yielded a *Staph. pyogenes* alone in three cases; in the remaining seven the infection was a mixture of *Staph. pyogenes* and a haemolytic streptococcus. The staphylococci were resistant to penicillin in one case and to chloramphenicol in two cases.

The 18 cases of sycosis barbae yielded pure growths of *Staph. pyogenes* alone. The staphylococci were resistant to penicillin in eight cases, to aureomycin in two, and to chloramphenicol in five.

The miscellany of eight cases of infected eczema, five cases of furunculosis, three cases of infective eczematoid dermatitis, and one case of blepharitis yielded a haemolytic streptococcus alone in one case, *Staph. pyogenes* in 14, and a combination of these organisms in two cases. Penicillin-resistant staphylococci numbered three and the organisms were sensitive to the other antibiotics.

Results

Impetigo.—Three cases were treated with base alone as a control; as expected, the impetigo spread rapidly. Of the remaining 45 cases treated with neomycin, 27 healed in less than one week, 11 in less than two weeks, and 7 took longer than two weeks, but were quite healed in three weeks. There were no failures. The cases varied in severity and duration. Twenty-one had resisted previous treatments by their own practitioners for over three weeks. Twenty-five cases were definitely known to have been treated with penicillin cream and six cases with chloramphenicol without response.

Sycosis Barbae.—The 18 cases are classified according to the severity and chronicity of the condition, those which had lasted less than nine months being referred to as folliculitis barbae. Eight cases of folliculitis barbae were seen whose duration varied from one week to eight months. Four of these cases are known to have been treated with penicillin cream, two with chloramphenicol cream, and one with aureomycin cream, all without success. On treatment with neomycin ointment four cases healed completely—two in less than one week, and two in a fortnight—and have remained healed for four months. One severe case improved to the extent of having only a few pustules left, and there was no response in three cases. The 10 cases of sycosis barbae varied in duration from two to 31 years. Six cases are known to have been treated with penicillin, five with chloramphenicol cream, and five with aureomycin cream, without cure. Four cases responded well to neomycin ointment, healing in periods ranging from two to four weeks, two of them having slight residual erythema but no pustulation while using the ointment. Two further cases healed in a fortnight, but relapsed

two and four months later while still using the ointment, although the organisms remained sensitive to the antibiotic. Two cases were much improved and two showed no response.

Ecthyma.—Of the 10 cases of pyoderma and ecthyma treated, 3 healed in less than one week; these were all cases in which *Staph. pyogenes* alone was cultured. The remaining seven cases had a mixed infection of staphylococci and streptococci, two healing in less than a fortnight and the other five showing no response.

Miscellaneous.—Eight cases of infected skin conditions, including seborrhoeic dermatitis, contact dermatitis, and eczema, were all treated without any sensitization reactions. Three cases healed in less than one week, four in two to three weeks, and one case showed no response. One case of chronic blepharitis healed in three days. Three cases of retro-auricular infective eczematoid dermatitis healed in less than two weeks. The five cases of furunculosis had resisted a variety of treatments for this condition, and only one case ceased to have boils on treatment with neomycin ointment.

Comment

In the treatment of impetigo contagiosa, neomycin ointment is effective and rapid in action. In view of the advantages of using neomycin as a solely local antibiotic it might with advantage be adopted as a routine treatment for this condition.

In this series 60% of cases of impetigo cleared in less than a week, and many of these took only three to four days. Forbes (1952) treated 67 cases of impetigo with neomycin, 62 clearing in less than a week; he remarks that the type of patient was of high standard, most of them being university students and able to follow instructions. It might be assumed that there is some difference in this capacity between American college students and the industrial population of Sheffield. In the treatment of impetigo, chloramphenicol cream (Newman and Feldman, 1951), aureomycin ointment (Solomons, 1951), and bacitracin (Miller *et al.*, 1949) all give comparable results, most cases healing in less than a week, though Solomons found two cases aggravated by aureomycin cream.

In the treatment of sycosis barbae, aureomycin cream seems to have given the best results. Solomons treated 22 cases, all of which responded, only three being left with a few scattered pustules. Chloramphenicol cream (Newman and Feldman, 1951) cured only one case in five, improved two cases, and gave no result in two. Bacitracin (Miller *et al.*, 1949) cured 5 of 16 cases, the other 11 showing no response. Neomycin ointment in this series cured eight cases, and improved five; there was no response in five. Neomycin therefore seems to be superior to all antibiotics except aureomycin in the treatment of this condition.

Prolonged local application of any antibiotic encourages the growth of resistant organisms, and in this series the only aureomycin-resistant staphylococci were found in two cases of sycosis barbae. The routine use of a purely local antibiotic would therefore seem desirable as the first line of attack in the treatment of this condition.

As a local application to infected skin conditions and infective eczematoid dermatitis, neomycin showed no tendency to irritate the skin. Over a large number of cases this harmlessness is unlikely to continue, but Kile *et al.* (1952) applied neomycin to 869 cases and obtained only one sensitivity reaction. In the same paper the authors remark that some patients with haemolytic streptococcal infections did not respond well to neomycin. This was also found in this series in the cases of ecthyma, though impetigo with streptococci responded well. In the cases of sycosis barbae which did not respond or which relapsed the organisms had not developed resistance to the drug. This state is unlikely to last, although it has been the experience of all other investigators of neomycin. Nevertheless, antibiotic therapy is literally becoming a process of hurrying to use the new drug before it ceases to cure.

Summary

Ninety-three cases of pyogenic skin disease were investigated bacteriologically; *Staphylococcus pyogenes* was isolated and found to be resistant to penicillin in 46 cases, to chloramphenicol in 18 cases, and to aureomycin in 2 cases. None were resistant to neomycin.

The cases were treated with neomycin ointment in a strength of 5 mg. per g. In the treatment of impetigo the drug gave results comparable to those of aureomycin, chloramphenicol, and bacitracin. In sycosis barbae the results were superior to those of all other antibiotics except aureomycin. In other skin conditions, with the exception of the deeper infections with haemolytic streptococci, infection was controlled and sensitization reactions were not encountered.

Neomycin ointment is suggested as a routine treatment for impetigo and as the first line of attack in sycosis barbae.

My thanks are due to Dr. J. Colquhoun for the bacteriological investigations. I am indebted to Dr. H. R. Vickers and Dr. I. B. Sneddon for permission to use their cases for this investigation, and to the Upjohn Company for the supply of neomycin and neomycin ointment.

REFERENCES

Forbes, M. A. (1952). *Sth. med. J.*, **45**, 235.
Kile, R. L., Rockwell, E. M., and Schwarz, J. (1952). *J. Amer. med. Ass.*, **148**, 339.
—— Welsh, A. L., and McAfee, G. D. (1950). *Arch. Derm. Syph., Chicago*, **62**, 911.
Kimberly, L. W. (1952). *J. Iowa St. med. Soc.*, **42**, 221.
Livingood, C. S., Nilasena, S., King, W. C., Stevenson, R. A., and Mullins, J. F. (1952). *J. Amer. med. Ass.*, **148**, 334.
Miller, J. L., Slatkin, M. H., and Johnson, B. A. (1949). *Arch. Derm. Syph., Chicago*, **60**, 106.
Newman, B. A., and Feldman, F. P. (1951). Ibid., **64**, 212.
Solomons, B. (1951). *British Medical Journal*, **2**, 525.
Waksman, S. A., and Lechevalier, H. A. (1949). *Science*, **109**, 305.

STORAGE OF TESTICULAR TISSUE AT VERY LOW TEMPERATURES

BY

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AND

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The discovery that glycerol has the property of protecting the spermatozoa of certain species (Polge, Smith, and Parkes, 1949; Smith and Polge, 1950) and also red blood cells (Smith, 1950; Sloviter, 1951a, 1951b) against the otherwise fatal effects of freezing and thawing was extended by Smith and Parkes (1951) to ovarian tissue. The latter work was recently recorded in more detail (Parkes and Smith, 1953), and it is clear that rat ovarian tissue, soaked in glycerol-containing media and subsequently frozen slowly and stored in liquid air, suffers only slight loss of its capacity to form an endocrinologically active graft. Moreover, the loss is not increased by prolonging very greatly the period of storage.

Method

Analogous observations have now been made on the preservation and grafting of rat testis tissue. The testes were taken from male rats 7 to 9 days old, at which age the organ is firm and easy to handle. The tunica was slit and the contents were slightly teased out. The capacity of such preparations to form functional grafts, after treat-

ment of various kinds, was tested by homoplastic grafting into the subcutaneous space of the flank in newly castrated adult rats. The tissue was grafted (*a*) without further treatment, (*b*) after soaking in 15% glycerol-saline, and (*c*) after soaking and cooling slowly in saline or 15% glycerol-saline to −79° C. (the temperature of dry ice) or −190° C. (the temperature of liquid air) for various periods, and thawing quickly at +40° C., according to the technique described by Parkes and Smith (1953) for ovarian tissue. Groups of 10 animals were used for each experiment. One or more animals in each group were killed at early stages, but the majority were allowed to live for three to four months after grafting, during which time a number of mating experiments were carried out. At necropsy the graft was removed for sectioning and the seminal vesicles were fixed and weighed. The gametogenic activity of the graft was assessed by its histological appearance, and its androgenic activity by the previous mating behaviour of the animal and the size of the seminal vesicles.

The histological development of these and other grafts of frozen testis tissue, especially in relation to spermatogenesis, will be dealt with in a paper by Dr. Deanesly. All that need be said here is that the endocrinologically active grafts recovered during the present series of experiments, whether derived from frozen or unfrozen tissue, resembled those usually obtained when testis tissue is grafted subcutaneously. The tubules were small and the interstitial and other intertubular tissue was prominent. The later stages of spermatogenesis were absent, but some tubules contained spermatocytes in active division. No regular difference was detected between established grafts derived from unfrozen tissue and those from tissue frozen in glycerol-saline.

Results

The experiments recorded here are summarized in the Table, in which the number of animals showing evidence of substantial androgenic activity on the part of the graft

Results of Grafting Rat Testicular Tissue Soaked and Frozen in Saline or 15% Glycerol-saline

Treatment	Time Tissue Frozen	No. of Animals Receiving Grafts	No. Developing Androgenic Grafts
Untreated	—	8	5
Soaked in glycerol-saline	Not frozen	8	5
Soaked in saline and frozen to −79° C.	One hour	6	0
Frozen to and stored at −79° C.	One hour	8	7
	One week	8	6
	8 weeks	5	2
	22 „	9	4
Frozen to and stored at −190° C.	One hour	16	14
	One week	10	8
	7 weeks	6	3
	22 „	9	7

Animals killed 12 to 16 weeks after receiving grafts.

is given in relation to the conditions and duration of freezing. It will be seen that tissue which had been frozen in 15% glycerol-saline and thawed formed an androgenic graft as readily as did unfrozen tissue, and that its viability did not obviously decrease on prolonged storage at low temperature. It appears that the difference between preservation in liquid air and in dry ice is not so marked as with rat ovarian tissue (Parkes and Smith, 1953). In considering the percentage of takes, it must be remembered that grafts showing only slight activity were not included in the right-hand column of the table, and that in all cases the grafts were homoplastic ones of some months' standing. In these circumstances the results with the tissue frozen in glycerol-saline must be regarded as promising.

The entry in the table for the grafting of tissue frozen in saline only should be amplified by recording that of the six rats kept for more than 12 weeks after implantation four developed small grafts, histologically recognizable as rudimentary testis tissue. The seminal vesicles, however, were completely atrophic macroscopically, and histological examination of the vesicular epithelium failed to provide evidence that the grafts had been even slightly active androgenically. The results were thus in strong contrast to those obtained with testes frozen in 15% glycerol-saline.

It seems, therefore, that the endocrine cells of the testis can be added to the list of tissues the prolonged storage of which at low temperatures is made possible, or greatly facilitated, by the use of media containing glycerol. It remains to be seen to what extent this technique may promote the use of viable transplants of endocrine and other tissue in man. Discussion of this problem will be found in the forthcoming volume of the Proceedings of the recent Ciba Symposium on the Preservation of Normal Tissues for Transplantation.

The operations and day-to-day observations were carried out by Miss J. Masson and Miss M. Mansi.

Summary

The androgenic tissue of the testis of the young rat can be preserved in viable condition for long periods by freezing in media containing glycerol, as previously described for the ovary of the rat (Smith and Parkes, 1951).

References

Parkes, A. S., and Smith, A. U. (1953). *Proc. roy. Soc. B*, **140**, 455.
Polge, C., Smith, A. U., and Parkes, A. S. (1949). *Nature, Lond.*, **164**, 666.
Sloviter, H. A. (1951a). *Lancet*, **1**, 823.
—— (1951b). *Ibid.*, **1**, 1350.
Smith, A. U. (1950). *Ibid.* **2**, 910.
—— and Parkes, A. S. (1951). *Ibid.*, **2**, 570.
—— and Polge, C. (1950). *Vet. Rec.*, **62**, 115.

Medical Memoranda

Intolerance to "Veriloid"

"Veriloid," a preparation of the alkaloids of *Veratrum viride* or green hellebore, is a potent hypotensive agent. Alarming symptoms from its use in moderate dosage occurred in the following case.

Case Report

A married woman aged 59, living alone, was admitted to Whittington Hospital at 9 p.m. on August 14, 1952, complaining of severe dull epigastric pain radiating upwards into the neck and down both arms; it had come on at 5 p.m. the same day. At the onset she had felt choked, vomited, and had some blurring of vision. She had been unable to get to her doctor for some time.

On examination she looked ill and her extremities were cold. The pulse rate was 40, regular, and the blood pressure was 80/60. The apex beat was displaced a little to the left; the heart sounds were normal. The fundi showed only slight arterial changes. There was no excessive salivation, and the pupils were of normal size. No abnormality was found in the lungs, abdomen, or central nervous system.

A provisional diagnosis of myocardial infarction was made, and she was given morphine ¼ gr. (11 mg.). The pulse rate did not rise above 60, and the blood pressure remained at 100/60 or less. The symptomatology was then reconsidered, and veriloid overdosage was thought more likely to have been the cause. She was therefore given atropine, 1/150 gr. (0.43 mg.). Her pulse increased slightly to 64, her blood pressure rose only to 115/80, but her pain ceased in the next hour and a half. At this point ephedrine, ½ gr. (32 mg.) was given by intramuscular injection. One hour later her pulse rate was 74 and her blood pressure 165/100. Electrocardiograms on August 15, 19, and 26 showed no abnormality. The white-cell count was 7,700 with a normal differential count, and the sedimentation rate was 8 mm. in one hour.

She remained well, up and about in the ward, with no return of pain or distress, from August 16 to 30, when she was discharged. Her resting blood pressure was then 200/110.

COMMENT

The patient had been taking two tablets of "veriloid–VP" three times daily after meals for six weeks before admission. The drug had been prescribed for hypertension, first diagnosed five years previously. Each tablet contains 2 mg. of veriloid and 15 mg. of phenobarbitone. On the day of admission she had had her last dose after lunch, and symptoms had occurred when she began her tea.

According to Kauntze and Trounce (1951), some patients taking 12 mg. of veriloid daily had toxic symptoms, including a substernal burning sensation (sometimes amounting to pain), salivation, globus or choking sensation, vomiting, coldness and tingling in the finger-tips, hiccup, and collapse. They stated that toxic symptoms are minimized by combining the veriloid with phenobarbitone and administering the tablets immediately after meals. In our patient the symptoms were so severe as to simulate myocardial infarction, and continued for several hours, but appeared to be controlled partially by atropine and, more effectively, by ephedrine. In a search of the literature we can find no reference to toxic symptoms so severe and protracted as these with moderate dosage of the drug.

Several authors comment on the narrow margin between therapeutic and toxic levels in some patients (Freis *et al.*, 1949; Kauntze and Trounce, 1951), but it is said that the emetic property of the drug precludes serious overdosage. Our patient vomited, but continued to have severe toxic symptoms for several hours. It is therefore clear that vomiting does not always occur in time to prevent very undesirable effects.

We would like to thank Dr. A. L. Jacobs, consultant physician, for permission to submit this case report.

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REFFERENCES

Freis, E. D., Stanton, J. R., Culbertson, J. W., Litter, J., Halperin, M. H., Burnett, C. H., and Wilkins, R. W. (1949). *J. clin. Invest.*, **28**, 353.
Kauntze, R., and Trounce, J. (1951). *Lancet*, **2**, 1002.

A Case of Meigs's Syndrome with an Ovarian Carcinoma

The association of hydrothorax, usually on the right side, with ascites and fibroma of the ovary was described in 1937 by Meigs and Cass, and since this time Meigs's name has become attached to this syndrome. This is not to say that he was the first to note such an association of clinical findings, for he quotes at length in a later article (Meigs *et al.*, 1943) a report by Lawson Tait (1892) of a typical example successfully operated on. Following Meigs's original article there has been a much more general recognition of the syndrome. Soon it became apparent that hydrothorax, usually on the right side, might occasionally be present in association with any marked ascites, whether caused by an ovarian tumour or cirrhosis of the liver, though the former was most commonly responsible.

There has been some discussion on the way hydrothorax is produced. The following case is reported as there seemed to be a fairly wide channel through which fluid passed readily from peritoneal to pleural cavity.

CASE REPORT

A married woman aged 52 was admitted to hospital on July 26, 1951, with marked ascites. Her haemoglobin being only 58%, 4 pints (2.3 litres) of blood was transfused over the course of the next few days. On July 31 she became dyspnoeic. I first saw her on the following day. Examination then showed a gross ascites, though no tumour could be detected on abdominal or vaginal examination. The right chest was dull to percussion, and an *x*-ray examination confirmed the presence of a pleural effusion. No underlying lung disease could be detected. A malignant ovarian tumour was suspected and laparotomy advised.

Before the operation repeated aspiration of the right chest was carried out. On August 1 36 oz. (1,020 ml.) of clear straw-coloured fluid was aspirated, followed by 38 oz. (1,080 ml.) two days later and 40 oz. (1,140 ml.) on August 11.

On August 13 the patient was anaesthetized and placed on the operating-table. Inspection then showed an obvious bilobar swelling lying more to the right side of the abdomen, while the ascitic distension had apparently disappeared. Laparotomy confirmed these findings except for a little ascites, which was cleared with sucker and mops. The upper pole of the tumour was then delivered through the incision. The lower pole was fixed by infiltration of the right ovario-pelvic ligament and adhesions to the rectum. By finger dissection enough mobilization of the tumour was obtained to allow the remaining pedicle to be clamped, and the tumour was removed. There was fairly profuse bleeding from the infiltrated area, and several clamps had to be applied to open gushing veins. Haemostasis was finally obtained, and, as the left ovary and uterus appeared normal and the complete removal of malignant tissue in the region of the pedicle was impossible, the abdomen was closed. There were no obvious secondaries in the omentum or on the peritoneum.

Blood transfusion was given post-operatively as there was some degree of shock, but there were no other complications, and the patient was discharged from hospital on August 29. She was referred for deep *x*-ray therapy, and received a full course of treatment. When last seen on November 15, 1951, she was well, there being no sign of recurrence, and no evidence of ascites or hydrothorax. An *x*-ray film of the chest showed no sign of pleural effusion or of metastasis.

Pathological Report.—"The specimen consists of a right ovarian cyst measuring 23 by 15 cm. Microscopically the appearances are those of a papillary adenocarcinoma."

COMMENT

The point of particular interest in this case is the considerable reduction in the amount of the ascites after aspiration of fluid from the chest. This seemed to indicate that there must be a fairly wide communication between these two cavities to allow so rapid a passage of such a large quantity of fluid. The presence of a persistent pleuro-peritoneal canal seemed to explain the features of this case most satisfactorily.

Meigs rejected his original suggestion that the right hydrothorax was due to lack of drainage by the azygos vein. He believed that a persistent pleuro-peritoneal canal was usually incompatible with life, and finally concluded that the fluid found its way through a lymphatic pathway in the diaphragm. This latter theory, however, would not account for the relative rarity of the occurrence of hydrothorax with ascites. Nor would it explain why the right side is favoured. It would, indeed, be reasonable to expect that a bilateral hydrothorax of some degree would occur in all cases of marked ascites.

A congenital opening, then, seemed to us to explain this syndrome most satisfactorily, and especially an opening resulting in a direct communication between the two cavities such as the persistent pleuro-peritoneal canal. Why, however, is the gap usually on the right side, while a diaphragmatic hernia through a persistent pleuro-peritoneal canal is usually on the left side? It is recognized that this type of hernia is uncommon on the right side, as the liver tends to occlude the right-sided openings. As herniation is then prevented, and as an opening on the left side usually results in a herniation incompatible with life, it is suggested that the more frequent occurrence of right-sided hydrothorax is due to lack of survival of those individuals whose persistent canal happens to be left-sided.

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REFERENCES

Meigs, J. V., Armstrong, S. H., and Hamilton, H. H. (1943). *Amer. J. Obstet. Gynec.*, **46**, 19.
—— and Cass, J. W. (1937). *Ibid.*, **33**, 249.
Tait, Lawson (1892). *Med.-chir. Trans.*, **75**, 109.

Reviews

BRITISH SURGEONS

Lives of the Fellows of the Royal College of Surgeons of England, 1930–1951. By the late Sir D'Arcy Power, K.B.E., F.R.C.S., and continued by W. R. Le Fanu, M.A. (Pp. 889. 42s. Obtainable from Editorial Secretary at the College.) London: Published by the College. 1953.

Plarr's *Lives of the Fellows* has for many years been a valuable work of reference and it is a pleasure to greet this continuation, which contains the lives of those Fellows whose death occurred between 1930 and 1951. Sir D'Arcy Power wrote the lives of those who died between 1930 and 1940, with one exception, and Mr. Le Fanu has written the remainder. Sir D'Arcy felt the loss of his friend Harvey Cushing so deeply that he thought he could not write an adequate life of this great man.

The volume contains the lives of 981 Fellows, among whom will be found the names of many of the most distinguished pioneers of modern surgery—Moynihan, Cushing, Grey Turner, Bland-Sutton, F. T. Paul, Arbuthnot Lane, Wilfred Trotter, James Berry, Tudor Edwards, Robert Jones, Thomson-Walker, G. H. Makins, and D'Arcy Power himself. There are also included a few physicians like Lord Dawson and Sir Humphry Rolleston, upon whom the Fellowship had been conferred.

This volume at once becomes the essential book of reference for most of the important British surgeons who moulded British surgery at a vital period of its growth. It gives the main facts of their lives, a list of their chief publications, and the sources from which further information can be obtained. Not only are their surgical deeds recorded but we are given illuminating details about what they did in their moments of relaxation, and it is interesting to note what were their pastimes. Many were fond of shooting and fishing, others were mountaineers, some were connoisseurs and collectors, some were musicians or photographers, some even worked embroidery, a few were ornithologists, one made a study of basking sharks, and several were yachtsmen, of whom one, Sir Alexander MacCormick, sailed his own craft from Australia to England with a crew whose ages were all over 60. Such activities have served to give relaxation from the surgical work that takes a heavy toll of these men in anxiety.

The reviewer spent the best part of a week-end reading a great number of the biographies and found them of engrossing interest. He had known, admired, and had an affection for many of these great pioneer surgeons, and his feelings of pride in their achievements were mingled with a sadness for their passing. Every Fellow of the College will surely wish to have a copy of this book upon his shelves.

ZACHARY COPE.

DIURESIS

Diuretic Therapy: The Pharmacology of Diuretic Agents and the Clinical Management of the Edematous Patient. By Alfred Vogl, M.D. (Pp. 248. £1 18s. 6d.) London: Baillière, Tindall and Cox. 1953.

An intelligent co-ordination of diuretic measures with proper attention to minor technical details may often restore an extremely dropsical patient to a reasonable state of health and comfort for a long time. Yet, though medical literature abounds in monographs on the pharmacology and therapeutic actions of digitalis, diuretic therapy, which is of almost equal importance, has received rather scant attention. The author of this scholarly but practical treatise was the first to observe the remarkable diuretic properties of the organic mercurials. It is of interest to note, as Dr. Arthur Fishberg points out in a foreword to the work, that the discovery of both digitalis and the organic mercurials was due to the prepared mind of the scientist being fructified by the observations of an attendant on the sick, or, to use the more modern language of bureaucracy, of a medical auxiliary—Withering's discovery owing much to Mother Hutton's success in the treatment of dropsy, and Vogl's to the accurate coloured charts of intake and output kept by an anonymous nurse on a patient undergoing treatment for syphilis with "novasurol." While this monograph is mostly concerned with the physiology, pharmacology, and clinical use of the organic mercurials in congestive heart failure, yet other diuretic measures such as treatment by acidifying salts, by low sodium intake, and by the xanthine and osmotic diuretics are not neglected, and the treatment of every type of oedema is discussed. The treatise is up to date, fully documented, and thoroughly readable, being written in good plain English.

D. M. DUNLOP.

PEPTIC ULCER

Peptic Ulcer: Pain Patterns, Diagnosis and Medical Treatment. By L. A. Smith, M.D., M.S. in Medicine, F.A.C.P., and A. B. Rivers, M.D., M.S. in Medicine, F.A.C.P. Foreword by George B. Eusterman, M.D. (Pp. 576; 208 figures. No price given.) New York: Appleton-Century-Crofts, Inc. 1953.

This book covers particularly the pain patterns, diagnosis, and medical treatment of peptic ulcer and is presented as a digest and evaluation of the experience of the Mayo Clinic in a series of 30,400 cases of peptic ulcer, ranging from the oesophagus to the ileum. The emphasis is particularly on the clinical aspects, with special reference to pain, and there are many illustrative diagrams and case histories. In addition, there are sections on the history of peptic ulcer and on the physiology of the stomach.

For those who are especially interested in peptic ulcer there are a number of interesting facets to the book, particularly in relation to ulcer pain, but it is a disappointing publication. It gives the impression that it was a long time on the stocks and was probably held up by the death of one of the editors (A.B.R.). Some of the chapters read as if they had been written some years ago. In the section on the treatment of bleeding, all of the 52 references are more than 10 years old, and in some other chapters too there is a paucity of recent references. Again, it is often difficult to get a clear picture of the personal opinion of the writers, which may become lost in a surfeit of reports from the literature.

Any book on peptic ulcer to-day must stand comparison with the recent monumental work by Ivy, Grossman, and Bachrach. This present publication lacks both the critical commentary and up-to-dateness which were so notable in that book.

F. AVERY JONES.

ATLAS OF HISTOLOGY

Pathology in Surgery. By Edwin F. Hirsch, Ph.D., M.D. (Pp. 647; 388 photographs; 2 colour plates. 76s. 6d.) London: Baillière, Tindall and Cox. 1953.

This is one of a number of annotated atlases of morbid histology published in the U.S.A. in recent years. The reason for their compilation is not far to seek, for the useful information provided by the examination of tissue removed at biopsy has gained for histological diagnosis an assured place in the investigation of an increasing number of diseases. The resulting demand for expert morbid histologists was at first impossible to meet, and these books were obviously written to help the increasing number of pathologists who wish to acquire diagnostic proficiency in a rather difficult art. Such proficiency can be gained only by long experience under expert supervision, free access to all kinds of morbid material, and the cultivation of a peculiar sort of visual memory of microscopic structure. There is no satisfactory alternative to this arduous discipline. Morbid histology must be learnt from the actual section, which, during the period of training, can never be replaced by photomicrographs, however good their quality.

These atlases are valuable for reference purposes for those who have enough experience to be able to read and interpret photomicrographs. They are positively dangerous to

the inexperienced morbid histologist, who may be tempted to diagnose the disease process by matching his section against the "picture in the book." Dr. Hirsch's volume is open to this criticism but to no other. It is entirely concerned with surgical diseases. The profuse illustrations are of good quality, well reproduced, and skilfully selected. The text is clearly written, and, although in places almost telegraphic in its brevity, it is packed with sound information and not a little pathological wisdom.

GEOFFREY HADFIELD.

EDINBURGH LECTURES

Edinburgh Post-graduate Lectures in Medicine. Volume 6, 1950–53. Published for the Honyman Gillespie Trust. (Pp. 508; illustrated. 21s.) Edinburgh and London: Oliver and Boyd. 1953.

This is the sixth volume of lectures delivered in the Royal Infirmary, Edinburgh, under the auspices of the Honyman Gillespie Trust. The thirty-four lectures have been evenly distributed over the whole field of medicine and surgery, and it is difficult to pick out any themes for special mention. Tuberculosis and diseases of the chest are best represented, and there are lectures on such new topics as A.C.T.H. and cortisone and the use of isotopes in diagnosis. There are two lectures on genetic subjects and a delightful article by McCrie entitled "Reflections from a Provincial Deanery." The volume is well produced and well illustrated, and contains some coloured plates. From the publishing point of view the price of 21s. is therefore extremely low.

L. J. WITTS.

BALLISTOCARDIOGRAPHY

Ballistocardiography: The Application of the Direct Ballistocardiograph to Clinical Medicine. By Professor William Dock, B.S., M.D., F.A.C.P., Harry Mandelbaum, M.D., F.A.C.P., and Robert A. Mandelbaum, B.A., M.D. (Pp. 293; 153 figures. £3 11s. 6d.) London: Henry Kimpton. 1953.

Ballistocardiography has not received much attention on this side of the Atlantic. This method of studying the action of the heart depends on the sum of several forces, and these may overlap one another or oppose one another. Briefly, three main actions may be distinguished: that of recoil when the blood is being ejected from a chamber; that of the impact of the ejected blood on the peripheral circulation, particularly on such a structure as the arch of the aorta; and, thirdly, the motion imparted to an elastic tube as a wave of pressure moves along it. When the movements which these forces impart to the body, lying horizontally, are recorded by suitable apparatus, several waves appear in the record, some 15 in all for each cardiac cycle. This sounds rather formidable, but it would appear that only five or six are important; others are not concerned with ventricular systole. The physical causes for some of these movements are admittedly hypothetical.

By this method the clinician is seeking to fill an important gap in knowledge which is to some extent filled by the examination of the pulse and of the heart beat itself. But the ballistocardiograph is much more sensitive than the fingers or ears. The reader will find the most interesting chapters are those on the effects of coronary disease on the function of the heart as expressed by the ballistocardiogram. Particularly notable are the sections on infarcts and on the diagnosis of angina pectoris. Striking alterations in the curves are obtained by exercise. Another interesting chapter is on the surprising effect of nicotine on the ballistocardiogram. The authors maintain that these effects may be noticed before any signs of disease appear. They have a number of patients who reacted in this way and later developed frank coronary trouble. The arrhythmias and defects of conduction are not well shown by this method.

The writing of the book is on the whole good; occasionally the expression is obscure, and too many lines pile up without a single stop. The illustrations are clear, but there are two criticisms. First, to the uninitiated it is most important to label the waves, for they are not easily distinguished, and for many of them there is no label at all, which makes it quite impossible to know which wave is which. Secondly, the timing is often given against pulse-tracings, and sometimes these hardly show up or do not appear on the record. It is much more satisfactory where the timing is done by the cardiogram. Anyone who wants to study this new subject will find the book useful. It is not really difficult, and there is something in it which might be well worth studying; but clearly a good deal of time will be needed to get the information. For instance, the suggestion is that on each occasion at least seven tracings will have to be taken, and some little time is required for the patient to settle down, and must also elapse after a meal. But if the claim is justified that "the ballistocardiogram gives information on the vigor and effectiveness of systole which no other technique can supply," then this information is certainly worth having.

TERENCE EAST.

SURGICAL HANDBOOK

Surgery of the Biliary Tract, Pancreas and Spleen: A Handbook of Operative Surgery. By Professor Charles B. Puestow, M.D., Ph.D.(Surg.). (Pp. 370; 72 plates. 68s. Subscribers to the whole series of Handbooks, 60s.) Chicago: The Year Book Publishers Inc. London: Interscience Publishers Ltd. 1953.

This is essentially a personal book and a practical book. The author addresses himself to surgical residents and to practising surgeons who may require guidance on procedures with which they are unfamiliar. He describes the methods he himself has found satisfactory and gives no bibliography.

It is inevitable that the views of a surgeon practising in another country should differ in some respects from those current in Britain. Dr. Puestow, for instance, favours needle biopsy in the diagnosis of cancer of the liver and of the pancreas. In biliary surgery he advocates division of the falciform ligament and use of the hepatic end as a tractor, and he displaces the liver medially in order to make the hilum more accessible. In exploring the common bile duct he seems to make a much longer incision in the duct than we should. He favours cholecyst-gastrostomy, which we have found unsatisfactory as a means of short-circuiting a biliary obstruction, and in pancreatectomy he seems to implant the gall-bladder rather than the common bile duct into the jejunum.

Common sense and practical experience mark his advice throughout. He points out the dangers of premature interference, and particularly of exploratory aspiration, in the treatment of subphrenic infections. He has found that the use of the bridge or the pillow in gall-bladder surgery does not improve access but is very apt to lead to troublesome backache afterwards. He reminds us that jaundice after an attack of gall-stone colic does not necessarily mean that a stone has entered the common duct. He devotes 150 pages in all to the surgery of the common duct, 40 of them dealing in an admirable manner with injuries and their repair. The surgery of cancer of the pancreas is discussed in a balanced manner, and the author has come to the conclusion, with which any experienced surgeon will agree, that in most cases only ampullary growths offer sufficiently good prospects of cure to justify the severe operation of pancreatico-duodenectomy.

The figures are all line drawings admirably chosen and executed, and showing the author's intention far better than the more elaborate half-tone figures that usually illustrate books on operative surgery. The experienced surgeon for whom this book is intended will find it interesting and useful.

HENEAGE OGILVIE.

In *Humanly Speaking* Dr. Eustace Chesser discusses fluently and provocatively sexual conduct in its social setting. He chooses for some of his main themes problems of adolescence, marriage and divorce, and society's attitude to the homosexual. Sir Cyril Burt contributes a foreword. The book is published by Hutchinson's Scientific and Technical Publications, price 8s. 6d.

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SICKLING AND MALARIA

The sickle-cell phenomenon has almost since its discovery been the subject of controversy. Until recently records of observation had tended to multiply much more rapidly than well-founded theories. Hypotheses were mutually contradictory, and even some series of recorded observations appeared incompatible with others. In the past two years, however, a body of well-established and generally accepted facts has begun to arise and to give a firm basis for theory.

Great numbers of Africans and many persons from other continents in normal health have red cells which, under chemically reducing conditions, form bizarre "sickle" shapes. These persons are said to have the sickle-cell trait. Other persons with similar (usually more severely distorted) red cells suffer from a chronic haemolytic anaemia associated with a high mortality: these are said to suffer from sickle-cell anaemia. It is important that the distinction should be made clinically and not as a result of genetical theories.

The two conditions taken together without distinction between them behave as a Mendelian dominant—every person showing sickling in any form has at least one parent who also shows it in some form. There is, moreover, evidence to show that most or all of the clinically normal persons with the trait are heterozygous for the condition, while most of the persons with sickle-cell anaemia are homozygous. This is the opinion of most workers in America and of many but not all of those who have worked in Africa.

The immediate cause of the sickling phenomenon and of the haemolysis of sickle-cell anaemia is the replacement of part or all of the normal haemoglobin of the red cell by a form of haemoglobin which, in the reduced state, has a very low solubility and crystallizes inside the cell. The sickle-cell-trait carrier (who is usually heterozygous) has less than 50% of this abnormal kind of haemoglobin, while most of the anaemic persons (usually homozygotes) have nearly 100% of it, usually with some of the foetal type of haemoglobin as well.

Whatever view be taken of the precise relation between the chemistry, genetics, and clinical manifestations of sickling, it appears that in many parts of Africa considerable numbers of persons are dying of sickle-cell anaemia. The gene for sickling is thus being eliminated, and unless some compensatory influence is at work the gene should ultimately reach an extremely low frequency. Two main alternative hypotheses have to be considered: either that the gene is maintained by a high rate of mutation from its normal allelomorph, or that heterozygotes for sickling tend to have more children than normal persons. The rate of mutation demanded is, as Dr. A. C. Allison points out in an article appearing elsewhere in this issue, three thousand times as high as that known for any other human gene: this hypothesis is therefore a most unlikely explanation. If sicklers are on the average to have more children than normal persons, then either individual parents must have more children or more sicklers must survive from birth to the reproductive age. The former possibility must be regarded as a reasonable one, for it has been shown for several other congenital diseases that parents tend, where possible, to over-compensate by subsequent replacement for the deaths which take place. Such compensation does not, however, depend solely on biological mechanisms but is largely dependent on cultural traditions. Thus, even if the process has a share in maintaining the incidence of sickling, it may be effective only in certain tribes. Selective survival, on the other hand, being a purely biological process would, if proved, be of more general application.

It was first suggested by Raper[1] that sickling was protective against tropical parasites, and later Brain[2] made the definite suggestion that heterozygous sicklers might have a greater resistance to malaria than normal persons. If this were so it would, by the operation of natural selection, tend to raise the frequency of sicklers in populations exposed to a high intensity of malarial infection. Impressed by the clinical evidence of Beet[3] and of Brain[2] and by the general correspondence between high malarial incidences in Africa and high sickling frequencies, Allison examined some hundreds of children of one homogeneous tribe for sickling and showed that the non-sicklers had a significantly higher rate of parasitaemia than the sicklers. In the course of the work he found important clues which suggested that sickling probably conferred a resistance which was specific to infection with *Plasmodium falciparum* rather than to malaria in general. He then infected with *Plasmodium falciparum* two carefully paired groups each of fifteen volunteers, one group consisting of sicklers and the other of non-

[1] *E. Afr. med. J.*, 1949, **26**, 281.
[2] *S. Afr. med. J.*, 1952, **26**, 925.
[3] *E. Afr. med. J.*, 1946, **23**, 75.
[4] *J. clin. Path.*, 1953, **6**, 329.
[5] *Man*, 1953, **53**, 9.
[6] Itano, H. A., *Science*, 1953, **117**, 89.

sicklers. The infection became firmly established in all but one of the non-sicklers, whereas only two of the sicklers became infected and then mildly.

In a problem where so many ill-defined variables are involved it is highly desirable that confirmatory investigations should be made by other workers and on other populations, but there can be little doubt that Allison has demonstrated that the possession of the sickle-cell trait gives considerable protection against *Plasmodium falciparum* infection, and that he has thus made clear the main mechanism whereby high frequencies of sickling are maintained in certain African, Indian, and Greek populations. Lehmann[4] and Allison have independently suggested that the relative protection against malaria which is enjoyed by newborn infants is due to the foetal type of haemoglobin in their red cells; and Allison has now shown that the progressively increasing incidence of malaria during the first year of life runs parallel to the replacement of foetal haemoglobin by the adult form. It may therefore further be suggested that in the child with sickling, in whom the foetal haemoglobin becomes largely replaced by the sickling instead of the normal adult form, this protection is to a great extent maintained, so that infection, when it occurs, as it almost inevitably will, is modified.

From now on the probability of a relation between sickling and malaria must be considered in investigations into the epidemiology of malaria in all parts of the world. Conversely, malarial incidence must be considered in all studies of the incidence of sickling. There is still a great need for such surveys as that carried out by Dr. H. Foy and his colleagues (see p. 294). While these authors do not regard malaria as an important factor influencing the distribution which they find, there is no doubt that the points which they stress, such as racial ancestry and genetic drift, have an important effect on sickling frequencies. Allison's work would, however, suggest that, provided the sickling gene is present in the population, its frequency will in the long run be determined mainly by the incidence of malaria. Nevertheless the presence or absence of sickling will remain an important anthropological character and a guide in the assessment of such hypotheses as that of Lehmann,[5] who suggests that the character was introduced into Africa by Veddoid immigrants.

Other widespread congenital abnormalities of haemoglobin synthesis are known—thalassaemia in the Mediterranean area, and the occurrence of haemoglobins C and D in American Negroes.[6] It is important that the distribution of these too should be studied and their possible relation to malaria and other infections explored.

THE PITUITARY AND CARCINOGENESIS

In 1945 Li, Evans, and Simpson[1] described the isolation of an anterior hypophysial growth hormone, and during the succeeding years, as supplies have become more readily available for research, some remarkable properties have been ascribed to this pituitary extract. The prolonged administration of growth hormone to rats causes more neoplasms to arise than would be expected to do spontaneously. They may affect the pulmonary and lymphatic tissues,[2] adrenal glands,[3] and reproductive organs.[4] Most laboratory animals, subjected as they are to interbreeding, are apt to produce strains which are particularly liable to develop malignant tumours in certain organs. Thus experimental work on tumour formation carried out in one animal farm may be difficult or impossible to reproduce in another even with apparently identical techniques.

Moon and his colleagues,[5] of the University of California, injected different strains of young mice for 194 days with up to 2.0 mg. of growth hormone daily. In only one strain did neoplasms arise. An interesting observation was that the females under this treatment grew larger than the controls, and developed larger viscera. Since the prolonged administration of growth hormone to rats produces tumours of various kinds in many different organs, it is clearly of interest to know what happens in such animals deprived of any growth hormone by hypophysectomy. These workers have shown that, after removal of the pituitary, rats do not develop spontaneous tumours, nor will the injection of growth hormone induce them to appear. In further experiments[6] pellets of methylcholanthrene, which is a potent carcinogen, were implanted into the gastrocnemius muscles of rats which had been hypophysectomized. The removal of the pituitary effectively inhibited the carcinogenic effect of the methylcholanthrene.

Another group of workers, Griffin, Rinfret, and Corsiglia,[7] studied the effect of hypophysectomy on the liver damage and hepatomas produced in rats by giving an azo dye with the food. They administered 3-methyl-4-dimethylaminoazobenzene to rats for ten to twelve weeks, and this induced a high percentage of liver tumours. Hypophysectomy effectively inhibited their developing. Further work[8] by these investigators at Stanford University showed that, if hypophysectomized rats fed on the azo dye were given

1 *J. biol. Chem.*, 1945, **159**, 353.
2 Moon, H. D., *et al.*, *Cancer Res.*, 1950, **10**, 297.
3 —— ibid., p. 364.
4 —— ibid., p. 549.
5 —— ibid., 1952, **12**, 448.
6 Moon, H. D., Simpson, M. E., and Evans, H. M., *Science*, 1952, **116**, 331.
7 Griffin, A. C., *et al.*, *Cancer Res.*, 1953, **13**, 77.
8 —— *Proc. Amer. Ass. Cancer Res.*, 1953, **1**, 21.
9 *Time*, February 1.
10 See *British Medical Journal*, 1953, **1**, 924.

A.C.T.H. or cortisone, no liver damage or tumour appeared, but, if they were given pituitary gonadotrophin, liver damage and cirrhosis were seen. It is possible that the pituitary factor or factors involved in this carcinogenic process are present in the gonadotrophic fraction. These recent experiments in carcinogenesis suggest very strongly that some pituitary factor must be present before a malignant change can be initiated in the body, though there must also be many other as yet unknown factors. It is striking that a known anterior pituitary fraction, the growth hormone, should induce malignant tumours in so many different organs of the rat when it is administered in excess.

Race, environment, diet, and injury mechanically or chemically induced have all been shown to be important in the causation of cancer in man. In addition, when malignant disease arises in prostate or breast it can sometimes be temporarily controlled by the administration of hormones. This hormone therapy consists in giving large doses of stilboestrol or testosterone, which inhibit the secretion of anterior pituitary hormones and possibly work by performing a "medical hypophysectomy." Since the initiation and also the continued growth of a neoplasm require the presence of a normally functioning anterior pituitary, and since many of the pituitary hormones are now available, hypophysectomy has become a possible method of treatment. This is borne out by a report in the current issue of *Time*,[9] according to which a Cuban woman seriously ill with recurrence of a breast cancer had her pituitary gland removed just over a year ago. She has had hormone-replacement therapy, and it is now reported that 95% of the outward signs of her cancer have disappeared. A few years ago it would have been considered most improbable that bilateral adrenalectomy would ever be advocated for arresting the growth of malignant disease in man,[10] but the introduction of cortisone has made this a feasible, if somewhat experimental, therapeutic procedure. Even if such drastic techniques as total adrenalectomy and hypophysectomy are restricted in the main to the experimental animal, they should in time help us to understand why malignant tumours grow in the way they do.

RESPIRATORY INFECTION AND EMPHYSEMA

It is an experience common to family doctors and hospital physicians alike that the winter months bring in their wake increasing numbers of patients with chronic bronchitis who, having developed an acute respiratory infection, suddenly become seriously ill and not infrequently die. These patients have signs of bronchopneumonia, are deeply cyanosed, mentally confused, and suffering from varying degrees of right heart failure: deterioration quickly occurs because they are already afflicted with emphysema, and their respiratory insufficiency is greatly aggravated by the added infection. The outcome in such patients is always difficult to forecast, but clinical impressions strongly suggest that the prognosis has been materially improved by the introduction of antibiotics and the efficient use of oxygen.

Elsewhere in this week's *Journal* Dr. T. Simpson describes his observations on 118 patients with acute respiratory infection complicating emphysema. The patients were mostly men in the sixth and seventh decades of life. The common occurrence of this malady can be judged from the fact that it was responsible for 4% of admissions to the medical wards and its seriousness from the fact that roughly one-third of the patients died while in hospital. Most patients had long-standing bronchitis and showed signs of bronchopneumonia, often complicated by mental confusion and heart failure. Among the notable features of complicated emphysema in this series of patients were a poor temperature response to infection, a fall in the systolic blood pressure on inspiration, and a curious appearance of the optic fundi characterized by darkness of the retina, distension of the veins, and changes in the optic disk sometimes amounting to papilloedema. Simpson believes that any respiratory infection in the emphysematous patient should be treated as an emergency. Antibiotic therapy is of paramount importance: penicillin is usually all that is required, but if that fails and chloramphenicol is also ineffective sputum examination will show to which of the other antibiotics the particular organisms are most sensitive. Hospital treatment will almost certainly be needed for those patients whose fever fails to respond quickly to treatment, or in whom deep cyanosis, mental symptoms, or heart failure supervene.

The administration of oxygen to these patients raises certain difficulties. It is generally agreed that relief of anoxia helps the patient, but it is now also known that mental confusion, myoclonic movements, coma, and even death can follow oxygen therapy.[1,2] The cause of these nervous symptoms has been investigated by Drs. E. K. Westlake and M. Kaye, whose observations are reported at page 302. They studied the effect of inhaling various

[1] Segal, M. S., and Dulfano, M. J., *Chronic Pulmonary Emphysema*, 1953. New York.
[2] Davies, C. E., and Mackinnon, J., *Lancet*, 1949, **2**, 883.
[3] *Physiologic Therapy in Respiratory Diseases*, 1948. Philadelphia.
[4] *J. Amer. med. Ass.*, 1950, **143**, 1047.

gaseous mixtures and found that the cerebrospinal-fluid pressure increased in response to both anoxia and carbon-dioxide retention (hypercapnia), the increased pressure probably being caused by increased cerebral blood flow. In most emphysematous patients with infection both anoxia and hypercapnia are present. The relief of anoxia, though in itself beneficial, also removes one of the stimuli to ventilation, and therefore further carbon dioxide retention takes place to offset the effect of oxygen therapy. Drs. Westlake and Kaye conclude that the adverse effects of oxygen therapy are due to the direct toxic action of carbon dioxide on the brain rather than to the raised intracranial pressure; and they do not believe in lumbar puncture as a method of treatment in patients with mental symptoms.

The use of oxygen in patients with respiratory infection must therefore be approached with a full knowledge of its dangers as well as its value. Simpson believes that Barach's method[3,4] of giving oxygen has some merit: here oxygen is given initially by nasal catheter, the rate of oxygen flow is slowly increased, and later the patient is transferred to an oxygen tent. The modern oxygen tent is the most efficient method of giving oxygen, but for this very reason the patient may develop cerebral signs of hypercapnia more quickly. Since respiratory depression will increase the dangers of carbon dioxide retention, morphine is strongly contraindicated in the infected emphysematous patient, and other sedatives must be used with great discretion.

AEROSOL DETERGENTS

The value of a humid atmosphere in the treatment of some forms of respiratory disease has long been recognized. Humidity is usually produced by means of steam or, more correctly, warm water vapour from a bronchitis kettle. In the patient's home a pan of boiling water on a stove may be used. The vapour is often "medicated" with tinct. benzoin co., which probably has little therapeutic effect although it does impart a pleasant smell to the atmosphere. The use of hot water vapour is not without its dangers, and there is some risk of scalding the patient or of producing hyperpyrexia in a sick child. In order to overcome these dangers various forms of "cold steam" humidification were devised in which cold water vapour was atomized by means of a spray,[1] and this method was thought to give a better effect more quickly. Now a recent development has been the use of various synthetic detergents, or wetting agents, in the form of an aerosol mist in order to liquefy viscid secretions.[2]

Detergents contain two radicals—a hydrophobic or water-repellent group, consisting of a long hydrocarbon chain, and a hydrophilic group. In aqueous solution the molecules arrange themselves so that the hydrophobic group is on the surface away from the water. The film which is formed lowers the surface tension and reduces the viscosity of the solution. In addition the hydrophobic group has some solvent action on fatty materials. A number of these substances in the form of mists have been tested both in experimental animals and in clinical practice. Hall tested four compounds for toxicity in guinea-pigs.[2] He found that if they were used in a concentration of greater than 0.1% dyspnoea was rapidly produced, and with higher concentrations the animals died. Post-mortem examination showed degeneration and desquamation of the alveolar epithelium, invasion of the alveolar spaces by macrophages, and fibroblastic proliferation. In a later clinical study Hall[3] investigated one compound—sodium lauryl sulphate—and recommended its use in concentration of 0.05% as an aerosol mist in exudative respiratory infections in infants. Small unpublished trials in this country have confirmed the absence of toxicity, but striking benefits have not been observed.

More recently another synthetic detergent—"triton W.R. 1339"—has been the subject of extensive investigation. The substance was first used as an aid to streptomycin inhalation in the treatment of pulmonary tuberculosis, and it was found to have a marked liquefying effect upon the sputum. Subsequently it was tried in various conditions characterized by excessive or thickened secretion from the respiratory tract and was found to be effective.[4] Ravenel has carried out studies on babies suffering from asphyxia neonatorum and claimed dramatic results.[5] Eighteen newborn infants suffering from massive atelectasis or from inhalation of liquor were treated, the diagnosis having been made on clinical grounds in most of the cases, only six being *x*-rayed before treatment; all eighteen recovered completely. Another six babies, four premature and two full-term, did not appear to be helped by treatment, but at necropsy two of them were found to have severe congenital cardiac malformations and another was reported to have "mesenchymal hyperplasia" of the lungs, with thick-walled alveolar septa. It was suggested that the aerosol detergent should be given prophylactically to newborn infants whenever the delivery has been difficult and respiratory complications are expected. Special nebulizers have been devised to deliver a fine dry mist, and Miller[6] describes a simple apparatus which he claims gives satisfactory results. The chief requirements are that the particles should be small (0.5 to 3 μ) in order to penetrate the alveoli. Larger particles are apt to be irritating to the respiratory mucosa and cause coughing and gagging. Apparatus that has been devised for giving penicillin by inhalation has also been found to give fairly satisfactory results. Ravenel has also given the indications for the use of aerosol detergents.[5] Among

1 Nelson, W. E., *Textbook of Pediatrics*, 5th ed., p. 215. Philadelphia, 1950.
2 Hall, G. C., *Amer. J. Dis. Child.*, 1950, **80**, 408.
3 —— ibid., 1952, **83**, 1.
4 Miller, J. B., and Boyer, E. H., *J. Pediat.*, 1952, **40**, 767.
5 Ravenel, S. F., *J. Amer. med. Ass.*, 1953, **151**, 707.
6 Miller, J. B., *Amer. J. Dis. Child.*, 1952, **84**, 616.
7 Craven, J. F., *J. Pediat.*, 1953, **42**, 228.
8 Limber, C. R., *et al.*, *J. Amer. med. Ass.*, 1952, **149**, 816.
9 Varga, C., and Wild, J., *Amer. J. Dis. Child.*, 1953, **86**, 273.

the conditions he has treated are laryngitis and laryngotracheobronchitis, where the results have been very good; asthma and allergic bronchitis; capillary bronchitis; pneumonia with atelectasis; whooping-cough; respiratory or bulbar paralysis in poliomyelitis; laryngeal oedema following bronchoscopy; and, most effectively, neonatal atelectasis.

No toxic effects have yet been reported from the use of triton W.R. 1339, and, unlike other detergents, it does not seem to cause haemolysis even in high concentrations. The product as put up for clinical use is a 0.125% solution combined with a 2% solution of sodium bicarbonate and 5% solution of glycerin. The last two solutions are said to stabilize the aerosol droplets and to assist in the liquefaction of mucus.

A different approach to this problem has been the use of proteolytic agents in aerosol form in order to liquefy tenacious sputum. Streptokinase and streptodornase have been used[7] with doubtful effect, but excellent results are claimed for the use of trypsin. Limber *et al.*[8] have used trypsin in the treatment of adults with chronic respiratory disease, and Varga and Wild[9] report a case of bulbar poliomyelitis in a child in which the use of this agent made the aspiration of secretion from the respiratory tract very much easier and there was considerable improvement in the patient's condition. Because trypsin is a protein there is some danger of sensitization reactions developing from its use, and antihistamine drugs have therefore been used in conjunction with it in order to minimize possible side effects.

So far there has been little experience in Britain of these forms of treatment. If the claims made for them can be substantiated, they would constitute a real advance in the treatment of acute respiratory disease in childhood.

DANGERS OF INDUCED HYPOTENSION

The effects of a low blood pressure on the reduction of bleeding during operations were known in the pre-anaesthetic era. In that dismal period surgeons hoped that their patients would faint early in the proceedings, not only because their pain would then cease, but also because haemorrhage became more controllable. After anaesthesia became an established practice, and until quite recently, it has been usual to try to maintain the blood pressure within normal limits, and for the surgeon to control the bleeding as he proceeded with the operation; if the blood loss became excessive it was made good by transfusion. In limb surgery a bloodless field could be secured by an Esmarch's bandage or other tourniquet, while in other areas a relatively avascular field could be obtained by infiltration with some vasoconstrictor solution such as 1 in 500,000 adrenaline in saline.

In the last few years, however, the idea of general hypotension to minimize bleeding was revived, and this was usually obtained in one of three ways. First, arteriotomy and bleeding might be carried out until the desired fall in pressure was obtained, followed by transfusion back of the same blood at the end of the operation; this amounts to induced haemorrhagic shock and is accompanied by vasoconstriction. Secondly, preganglionic sympathetic block might be obtained by high subarachnoid or peridural spinal analgesia. Or, thirdly, ganglionic sympathetic and parasympathetic block might be induced by the intravenous injection of a methonium or thiophanium derivative combined with suitable posture. The last two techniques entail vasodilatation. All these methods are effective in producing hypotension, although the adjective "controlled" is open to question. Relatively ischaemic fields were welcomed particularly by plastic and cranial surgeons, and the practice of the technique was spreading rapidly, when it became clear that a heavy price was being paid in fatalities and severe post-operative complications.

The question of the frequency of these unfortunate consequences then arose, and a determined effort to find the answer was made by Hampton and Little.[1] These investigators sent questionaries to 602 members of the Association of Anaesthetists of Great Britain and Ireland, and received back completed reports from the surprisingly high number of 299 anaesthetists. In brief, this investigation showed that in 21,000 cases of induced hypotension 46 fatalities occurred, of which 42 were probably associated with the technique (one death in 500 cases). Non-fatal complications affecting mainly the cerebral, renal, and coronary circulations occurred on 549 occasions (one in 38 cases). A similar inquiry circulated to diplomates of the American Board of Anesthesiologists showed 50 deaths in 6,805 operations (one death in 136 cases). An interesting result of the latter investigation was that a significantly greater number of complications occurred if the blood pressure was allowed to fall below 80 mm. Hg. Too much must not be deduced from these results in the absence of control cases, but it is evident that induced hypotension does carry a considerably greater risk than normal methods of anaesthesia. Two comprehensive surveys based on all available evidence were made by Armstrong Davison[2] and Woolmer.[3] The general conclusion was that the technique of induced hypotension should not be used except for operations essential to avert death or really serious disability and impossible to perform without a bloodless field.

The general acceptance of the view that hypotension was too risky for general use has stimulated investigators to find out means of making it safer. The most promising line of research appears to be that of reducing the basal metabolic rate so that a reduced oxygen supply is still sufficient for the vital organs. Delorme[4] has pointed out that this can be accomplished by hypothermia but that superficial cooling in adults provokes the natural response of shivering, and this must be suppressed either by deep anaesthesia, muscle relaxants, central cooling by means of an arterio-venous shunt, or by one or other of the inappropriately named "lytic cocktails" which contain various

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1 *Arch. Surg. (Chicago)*, 1953, **67**, 549.
2 *Anaesthesia*, 1953, **8**, 255.
3 *Lancet*, 1953, **2**, 190.
4 Ibid., 1952, **2**, 914.
5 *British Medical Journal*, 1953, **2**, 1256.
6 *Lancet*, 1953, **2**, 1294.

derivatives of phenothiazine such as promethazine and chlorpromazine. These techniques were recently discussed at a meeting of the Section of Anaesthetics of the Royal Society of Medicine and in these columns.[5] With these varied aids it is possible to reduce the B.M.R. almost to zero for a short time, as with a cut-off cardiac inflow for intracardiac surgery. A few successful cases have been reported in the human subject, but the high degree of cooling and hypotension necessary are undoubtedly dangerous and may lead to irreversible ventricular fibrillation when attempts are made to restart the heart at the end of the operation. In these exceptional cases it is probably better to use a moderate degree of hypothermia (not below 28° C.) and a shunt carried out by means of a heart-lung machine (or pump oxygenator) as described by Melrose.[6] All this work is unquestionably still in the experimental stage, and individual anaesthetists not connected with a research unit would best rely on well-proved methods, which are suitable for all but very exceptional cases.

MEDICAL AUXILIARIES

Last week we briefly described the regulations[1] which are to come into force on April 1 laying down the qualifications required for medical auxiliaries in the National Health Service. The regulations are stated to be based upon the recommendations made by the Cope Committees in 1951, but, "to avoid certain anomalies and unfairness," those recommendations have not been applied strictly. The question of statutory registration, which was also recommended by the Cope Committees, is to be considered by a working party with a view to "evolving a scheme which will be acceptable" both to the Minister and to the medical auxiliaries.

Many of the qualifications set down as acceptable at present are in accordance with the recommendations of the Cope Committees, but there are important variations in the qualifications of the physiotherapists and the chiropodists. The most important body of physiotherapists is the Chartered Society, which lays down that there shall be a course of training lasting three years. One of the qualifications recognized by the Minister falls short of this standard, and it is to be hoped that after April 1 such lower standards will not be acceptable. A departure from the recommendations of the Cope Committees occurs also in the matter of qualifications required for chiropodists.

Some months ago we emphasized[2] the need for State registration and for the setting up of a central authority to co-ordinate the various medical auxiliaries. Statutory registration is now the rule for doctors, dentists, nurses, and midwives, and it surely ought to be the rule for medical auxiliaries, who have been growing in numbers and influence during the past decade. There are several groups of professional workers in the National Health Service who are asking for recognition, and a central council is needed which will be competent to judge whether recognition should be granted to these. At the same time such a council would be the appropriate body to maintain a statutory register of all medical auxiliaries and be the final arbiter on the adequacy of the various curricula. It is to be hoped that the working party to be appointed by the Minister will bear these points in mind. There is now undoubtedly an opportunity for the Minister to achieve a piece of constructive statesmanship which will bring the position of medical auxiliaries into line with the other professions in the National Health Service.

[1] See *British Medical Journal*, January 30, 1954, p. 284.
[2] Ibid., 1952, 1, 1267.

ANTIBIOTICS AGAINST NEOPLASMS

In a search for effective chemotherapeutic agents inhibiting malignant tumours experimentalists have, during the last few years, included antibiotics in their list of substances for screening tests.[1] This was a rational procedure, for Gale[2] has shown that chloramphenicol, aureomycin, and terramycin inhibit protein synthesis, and bacitracin inhibits protein and nucleic-acid synthesis in *Staphylococcus aureus*—activity that is desirable in a compound to be used against neoplasms. An outstanding problem, however, is to find such a preparation with selective toxicity against tumour cells as compared with normal cells, a difference which fortunately exists so often between the effect on parasites and that on the infected host. The sixth International Microbiological Congress, held in Rome in 1953,[3] heard a report by Waksman on the effect of actinomycin C on tumours as observed by Domagk. Now comes the news that American workers[4] have isolated from another strain of streptomyces an amino-acid derivative, L-azaserine. The director and some of his colleagues at the Sloan-Kettering Institute for Cancer Research in New York report[5] that this peculiar product shows a remarkable effect on the transplanted mouse sarcoma 180. Further details of other findings are promised. What does this portend for the treatment of human neoplastic diseases? Will it signify a turning point in the development of therapeutics against cancer and reticuloses such as the discovery of sulphonamides and penicillin did in the treatment of microbial infections? It is hoped that patients suffering from reticuloses might be the first to benefit from the new antibiotic. Its discovery will in any case stimulate further search among fungal products and give a possible lead to the synthesis of suitable agents. The question arises immediately whether the selective action of such material against pathologically proliferating blood elements compares favourably with that of nitrogen mustards, T.E.M., mercaptopurine, "myleran," and other experimental drugs at present in use against lymphatic or myeloid, acute or chronic, forms of leukaemia. Those engaged on this work are well qualified to find the answer quickly to these urgent questions.

[1] Reilly, H. C., *et al.*, *Cancer Res.*, 1953, **13**, 684.
[2] Gale, E. F., and Folkes, J. P., *Biochem. J.*, 1953, **53**, 493.
[3] Waksman, S., *6th Internat. Microbiological Congress*, p. 3–12. 1953.
[4] Bartz, Q. R., *et al.*, *Nature, Lond.*, 1954, **173**, 72.
[5] Stock, C. Chester, *et al.*, ibid., 1954, **173**, 71.

CLINICAL PATHOLOGY IN GENERAL PRACTICE

THE NORMAL BLOOD COUNT

BY

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A blood count offers figures from which the clinician hopes to confirm his diagnosis. Unfortunately, the errors in even the best-conducted blood count are enormous, and in an expert's hands a determination of haemoglobin and an examination of a stained film are usually more informative.

Haemoglobin Level

Methods.—The estimation of haemoglobin is done by one or other colorimetric method, nowadays usually comparison of dilute (1 in 200) oxyhaemoglobin with a grey screen, viewing both through a green filter (M.R.C. photometer) or photoelectric determination of the absorption of light by a dilution of blood in water (oxyhaemoglobin) or in N/10 NaOH (alkaline haematin). The classical Haldane method is dying out because of its inherent inaccuracy, although it and the M.R.C. photometer are the only methods which can be calibrated by the National Physical Laboratory.

Reproducibility.—The modern methods are about as accurate as are the graduated pipettes used for them. In time past, the errors of calibration of haemoglobin pipettes were great: nowadays they are usually bought to British Standard Specification No. 797 and tolerance is ±3%, so that a series of replicates taken from a bottle of blood will vary by no more than this. Unfortunately, replicates taken from a patient at different times vary much more than this, for any individual may show fluctuations of 7% in his haemoglobin level. A convenient estimate is that two estimations of haemoglobin made at different times on the same patient differ significantly if the difference exceeds a tenth of the average of the two determinations. The old Haldane method is much less accurate than are the modern methods mentioned above, and with this method the difference should exceed 15% for it to be significant.

Standards.—It was only during the war that E. J. King in London and R. G. Macfarlane in Oxford discovered that Haldane's original calibration of his "100%=13.8 g." standard had been inaccurate, and that the 100% Haldane standard actually corresponded to 14.8 g. haemoglobin per 100 ml. This explained a series of observations which had puzzled haematologists—for example, why Americans appeared to average about 1 g. haemoglobin per 100 ml. more than Englishmen. The new Haldane calibration is that 100%=14.8 g. per 100 ml. The Medical Research Council has recently organized a scheme whereby samples of blood of accurately known haemoglobin content are supplied at regular intervals to large laboratories so that they can standardize their instruments. With this and a secondary standard such as a grey glass or wire mesh screen, a haemoglobinometer can be maintained in accurate calibration for years, even if a photoelectric cell has to be changed at short notice.

Normal Values.—For men these can be taken as 14.8±1.5 g. per 100 ml. (13.3–16.3 g.) or 90–110%, which will include more than 19 out of 20 normal subjects. Occasionally normal subjects have lower or higher figures than this, but such subjects are rare: only about 1 in 300 have values below 12.6 g. or over 17 g. (85%–115%). For women, the level chosen depends on the definition of normal. If "normal" is equated to "optimal," then the level for women is the same as that for men; but many women can maintain this only when their average iron intake is much greater than normal—some 30–60 mg. in place of the usual 10–15 mg. If "normal" is equated to "usual," however, the range extends much lower: it is quite common to find apparently healthy women with haemoglobin levels of 85% or even 80% (12.6 or 11.8 g. per 100 ml.). Such women nearly all show a rise to levels within the male range if they receive a supplement of 65 mg. ferrous iron daily for 30–60 days (one ferrous sulphate compound tablet, *N.F.*), though they often fall again as soon as the iron supplement is withdrawn. In such women the menstrual loss is usually excessive or the diet is poor.

Mean Corpuscular Haemoglobin Concentration

The packed cell volume (P.C.V.) indicates the percentage of the volume of the blood which is occupied by the red cells; it is determined with the haematocrit. The standard practice is to collect venous blood into Wintrobe's anticoagulant (potassium and ammonium oxalate) and centrifuge a sample in Wintrobe's haematocrit tube for 30 minutes at 3,000 r.p.m. The normal range for men is 42–48% (mean 45%) and reproducibility is about the same as for the estimation of haemoglobin. Estimation of the P.C.V. gives the same sort of information as does that of the haemoglobin—in fact, one is often substituted for the other, but usually the haemoglobin is slightly more informative. The two estimations can, however, be combined to yield an index of great value—the mean corpuscular haemoglobin concentration (M.C.H.C.), obtained by dividing haemoglobin concentration expressed in grammes per litre by the percentage of blood occupied by cells (P.C.V.). The M.C.H.C. is a direct indication of iron deficiency. Most normal subjects have M.C.H.C. values between 32% and 35%; patients with marked iron deficiency have values below 30%, while values between 30% and 32% may occur in normal subjects, but are suggestive of mild iron deficiency. Because haemoglobin and P.C.V. can both be determined with high and comparable accuracy, the M.C.H.C. is subject to quite a small experimental error, and is reproducible with a high degree of consistency.

Red-cell Count

The red-cell count is greatly overrated as a diagnostic aid, because the errors inherent in it are immense and the labour required by it is considerable. First, the tolerance on volume in the counting chamber is ±5%, and that of dilution pipettes ±3%, so that duplicate counts by different workers could be performed with instruments differing by as much as 16%. So extreme a variation would, of course, be rare, but in addition to this error of calibration is the uncertainty due to chance variations in the number of cells which settle on unit area; this random error was computed theoretically as long ago as 1879 and demonstrated practically in 1881: it is enormous.* Thus if a count of 4,000,000 per c.mm. is estimated by counting 400 cells, then there is 1 chance in 20 that the true count is less than 3,600,000 or more than 4,400,000. This range can be reduced only by counting more cells: it is halved whenever the number of cells counted is increased fourfold.

In my own laboratory I deprecate the performance of red-cell counts unless 1,000 cells are counted; my clinical colleagues rarely insist on counts when they appreciate how unreliable they are and how much labour they require.

*One count in every 20 may be expected to lie more than $(200/\sqrt{N})\%$ from the true value, where N is the number of cells counted: if N=400, then $200/\sqrt{N}=10\%$.

Colour Index

There are three indices which depend on the red-cell count and share with it its unreliability: (1) The colour index (C.I.) (Hb, expressed as percentage of normal÷red cells, expressed as percentage of normal; or, since normal red blood cells approximate 5,000,000 per c.mm., Hb%÷20×red-cell count in millions per c.mm.). (2) The mean corpuscular haemoglobin (M.C.H.), which is the average Hb content of a cell (Hb contained in 1 ml. blood÷1,000×red cells per c.mm.: mean 29×10^{-12} g. or 29 γγ). (3) The mean corpuscular volume (M.C.V.), the average volume of a cell, computed from P.C.V. and red-cell count, as follows: P.C.V.÷10×red cells in millions per c.mm. The normal M.C.V. lies between 82 and 95 μ^3. Of these three indices the M.C.V. is the most important.

The colour index and M.C.H. do not discriminate between the volume of a cell and the concentration of haemoglobin therein. For example, a patient's count might be Hb=42% or 6.2 g., red cells=2,000,000 per c.mm., P.C.V.=24%, when C.I.=1.05 and M.C.H.=31.2 γγ, well within the normal range, leading to a diagnosis of simple or aplastic anaemia. When the M.C.V. is found to be 120 μ^3, considerably increased, and the M.C.H.C. is 26%, a subnormal value, one is led to consider a combination of pernicious and iron-deficiency anaemias—a combination less rare than might be expected and quite clearly shown in the stained film. It is its inherent inaccuracy and inability to discriminate between changes in volume and changes in haemoglobin concentration which has made haematologists spurn the colour index and adopt instead Wintrobe's "absolute indices," which facilitate precise diagnosis by separating volume changes from changes in concentration of haemoglobin within the cell. Personally, I usually reduce labour by estimating Hb and P.C.V., computing the M.C.H.C. to assess the degree of iron deficiency, and examine a film to exclude gross changes of size and shape in the cells: I find that only about one erythrocyte count need be performed for 12 to 15 determinations of haemoglobin.

Price-Jones Curve

An index of great value, which is unfortunately too expensive to perform as a routine, is the Price-Jones curve. This is performed by classifying cells according to their average diameter, and drawing the curve showing how frequent are the cells of different sizes. A normal blood yields a symmetrical narrow-based curve because the variation in size of cells (anisocytosis) is small. Severe iron-deficiency anaemia yields a curve in which the peak has moved to a smaller diameter and the base is wider because cells are more variable (anisocytosis increased): pernicious anaemia yields a relatively flat curve, with a peak shifted to a higher diameter and a very wide base (gross anisocytosis). Price-Jones curves are at present mainly of academic interest, though they may become a routine investigation when a new automatic particle counter and measurer comes into use, because this instrument should allow red-cell counts to be done automatically on several thousand cells, which could also be classified automatically into groups differing in diameter by about 1 μ.

The halometer, introduced by Pijper, of Pretoria, is a convenient instrument by which the modal cell diameter ("peak of the Price-Jones curve") can be measured accurately, and the degree of variation in size can be roughly assessed. There are many instruments available, but the simplest is that of the Association of Clinical Pathologists: it consists of a board on which are fixed two flash-lamp bulbs 28 in. (71 cm.) apart. If a thin blood film is held to the eye while looking at the bulbs in a darkened room, each light is seen to be surrounded by (from within outwards) a yellow halo, a dark zone, and a circular rainbow, the red being outside. The observer moves to and from the lights in a line perpendicular to that joining them until the outer edges of the two circular rainbows just touch. The distance from the blood film to the midpoint between the lights, measured in feet, is equal to the modal cell diameter (peak of Price-Jones curve) in microns. Three unstained films should be measured. If anisocytosis (variation in size) is marked, the rainbows will be less distinct, and in severe pernicious anaemia anisocytosis may be so great that the rainbow cannot be clearly seen and the halometer cannot yield any measure of cell diameter, though even here it does inform one that anisocytosis is excessive.

The ingenious practitioner can devise his own halometer: in emergency I have made a white mark on brown cardboard, made a pencil hole 14 in. (35.5 cm.) from the mark, and hung the card in front of an electric light: I retire until the red of the rainbow touches the white line; then my eye is N feet from the hole, where N is the modal cell diameter of the specimen of blood.

Appearance of the Red Cell

The measures so far considered permit one to estimate the concentration of haemoglobin in the blood, and the size and haemoglobin saturation of the cell. The shape of the cell has been considered only in relation to the Price-Jones curve, and its functional activity not at all.

The shape of the cell is best assessed by examining a stained blood film which is so thin that the cells are separate. Variation in size is described as anisocytosis; it is slight in normal subjects, moderate in iron-deficiency anaemia, and extreme in pernicious anaemia. Misshapen cells are called poikilocytes, and if they are numerous poikilocytosis is said to be present and is always an indication of serious haematological disorder. An estimate of whether the cell tends to be larger than normal, about normal size, or smaller than normal can be made by eye, and these are described by the terms macrocytosis, normocytosis, and microcytosis respectively. If the film is well stained the peculiarities of staining can be seen: when the normal cell is a pinkish yellow, a few cells of slaty blue colour can sometimes be seen; if the colour is uniformly distributed, the cell is polychromatic (shows polychromasia) and polychromatic cells appear to be the same as reticulocytes. Sometimes the slaty blue colour is due to the presence of dots of blue pigment—that is, of methylene blue or other basic dye from the stain—and this is punctate basophilia, common in marked anaemias but rare in the absence of gross anaemia except in patients with lead-poisoning.

The well-stained normal red cell shows a slight central pallor, where the biconcavity is evident. Sometimes this is absent, when it is usually due to bad staining, though occasionally the cell may have a smaller diameter than usual and show no central pallor—this is described as microspherocytosis and is constantly found in congenital haemolytic anaemia (acholuric jaundice) and during haemolytic crises in haemolysinic haemolytic anaemias. The central pallor may increase (hypochromia) until a narrow pink rim surrounds an unstained centre—the pessary cell of severe iron deficiency. Sometimes the periphery and the centre of the cell stain densely, but there is a zone of pallor between the two; this is the target cell, or Mexican hat cell, found in obstructive jaundice, in the severest iron-deficiency anaemia, in Mediterranean anaemia, and in sickle-cell anaemia; it is an abnormally thin cell, a leptocyte, the opposite of a spherocyte.

Typical mild or moderate iron deficiency shows no such extreme change. Some cells show increase in the central pale area, and such cells are usually rather small, but there are always normally staining cells of normal size present; if the size of the central pale area varies greatly from cell to cell, one may speak of anisochromia; this is a very sensitive indication of iron deficiency even if anaemia is only slight.

Some blood samples show other peculiarities of importance. Reticulocytes may be constantly increased in conditions in which blood cells are being produced more rapidly than normal, particularly in haemolytic anaemia and in

leuco-erythroblastic anaemia. Heinz bodies are refractile bodies detected within the erythrocyte after supravital staining: they appear after administration of haemolytic poisons such as phenylhydrazine, but can be produced *in vitro* by the action of ascorbic acid. Pappenheimer bodies are basophilic bodies seen in the red cells in rare forms of haemolytic anaemia. Siderocytes contain granules in which iron can be demonstrated. Howell-Jolly bodies are basophilic bodies 0.2–0.5 μ in diameter derived from chromosomes which have failed to fuse with either nucleus because they became separated from the mitotic spindle. They are particularly common after splenectomy, and are not rare in pernicious anaemia.

There are a few congenital diseases which must be mentioned. In some patients the erythrocytes are elliptical (elliptocytosis), in others crenated: both conditions may be associated with an increased rate of red-cell destruction. They are of considerable genetic interest and should always be referred to a specialist in genetics. In patients with thalassaemia (major or minor) many cells are target cells, and foetal haemoglobin persists in adult life. In sickle-cell trait or anaemia cells appear in films as target cells, but when reduced *in vitro* or *in vivo* the cell elongates and may throw out long terminal filaments; the change occurs because an abnormal haemoglobin is present and its reduced form is almost insoluble and crystallizes out. Since the Mediterranean trait (thalassaemia minor) may have a frequency of 20% in some populations (Cyprus) and sickle-cell trait 50% in others, such as the East African pigmoids, in certain areas they may come to be regarded as "normal"—that is, usual. There are other congenital anomalies involving leucocytes—hypersegmentation, or Alder's anomaly, and failure of segmentation, the Pelger-Huët anomaly—but these are extremely rare in all populations.

The Normal Blood Count

Haemoglobin		12–17 g. per 100 ml.
Erythrocytes		4.3–6.4 mill./c.mm.
Haematocrit		42–48%
M.C.V.		82–95 μ^3
M.C.H.C.		30–35%
Reticulocytes		0–2%
Total leucocytes		4,000–9,000 per c.mm.
Neutrophil	Juvenile	0–100 per c.mm.
	Staff	0–500 per c.mm.
	Segmented	2,500–6,000 per c.mm.
Eosinophils		0–400 per c.mm.
Basophils		0–100 per c.mm.
Lymphocytes		1,000–3,000 per c.mm.
Monocytes		0–800 per c.mm.
Platelets		250,000–500,000 per c.mm.

The White Blood Cells

There are five or six different types of cell included under the generic term leucocyte, and each appears to have a special function. It is the absolute rise or fall of each type which is important, not the proportion which that type bears to the total. This makes it essential to express the differential count as N cells per c.mm.—the absolute count—and not as a percentage as was once the practice. In this way the analysis of a count is actually simplified. If one blood sample showed a leucocyte count of 20,000 and a second a count of 2,000 per c.mm., and both had differential counts of 20% neutrophils and 70% lymphocytes, one would have to think carefully to realize that in the first blood the neutrophils are normal and the lymphocytes greatly increased (suggesting pertussis) and that in the second the neutrophils are greatly reduced. If one sees the counts expressed as: (1) neutrophils 4,000, lymphocytes 14,000 per c.mm.; (2) neutrophils 400, lymphocytes 1,400 per c.mm.; the difference at once leaps to the eye.

The neutrophil polymorphonuclear cells in resting normal adults range from 2,500 to 6,500 per c.mm. The ordinary neutrophil has a segmented nucleus. Some 10% of neutrophils have, however a nucleus with the form of a bent rod without constrictions: these are the "staff forms" or "stab-kernige" cells, a slightly less mature form; and about 1% of neutrophils have a kidney-shaped nucleus—the "juvenile" or metamyelocyte stage.

The neutrophils increase (1) on exercise—walking about may cause a rise of 500–1,000 and violent exercise a rise of 20,000–30,000; (2) irregularly during pregnancy, though rarely to above 10,000 per c.mm.; (3) when tissue is breaking down, as a result either of trauma or of necrosis due to infarction or to infection.

The eosinophil polymorphonuclear cells are usually said to range from 0 to 200 in normal subjects. Recently techniques for direct counting in a haemocytometer have been developed, and these are far more precise than the differential count; the new techniques reveal a few counts in normal subjects up to 800 per c.mm., and analysis suggests that there is no definable upper limit of normal,* although counts over 600 per c.mm. are more likely to be abnormal than normal. Eosinophils are increased in a variety of conditions in which foreign proteins enter the body—the allergic diseases (asthma, hay-fever, and some eczemas), infections with trichinellae and ascarides while the larvae are passing through the body, some abnormal antigen-antibody reactions such as exfoliative dermatitis, and collagen diseases in some patients.

The basophil polymorphonuclears number 0–100 per c.mm. and are of uncertain function.

The lymphocytes appear to be involved in the production of antibodies. Normally they number 1,500–3,000 per c.mm. and are increased in infancy to 4,000–6,000 per c.mm.; they are also increased in whooping-cough, acute infectious lymphocytosis, and lymphatic leukaemia. Abnormal lymphocytes characterized by foamy cytoplasm and an immature nucleus are numerous (500–10,000 per c.mm.) in glandular fever, and occur in smaller numbers in a variety of virus infections, notably in infective hepatitis, as well as in normal infants during the first 14 days of extrauterine life.

The monocytes are normally 0–800 per c.mm.; they are increased in the recovery phase of acute infections and in many chronic infections.

The sum total of the leucocytes is very variable, but in young men at rest it varies between 3,600 and 8,000 per c.mm., with a very few as low as 3,100 or as high as 9,300. Diurnal variation averages 1,600, but may reach 2,500. There is a slight rise between noon and 3 p.m., but no true digestive leucocytosis. The neutrophilia of exercise and of other conditions is reflected in the total leucocyte count. In infants of over 3 months and children under 4 years, lymphocytes exceed the neutrophils and may reach 6,000 per c.mm.; these two cell types are equally numerous by the age of 4 years, and thereafter slowly progress towards adult levels.

Platelets range from 200,000 to 500,000, the range varying somewhat according to technique. Increases are common in polycythaemia rubra vera and chronic myeloid leukaemia, decreases in thrombocytopenic purpura, acute leukaemia, and, more frequently each year, as a result of the administration of drugs.

Next article on Clinical Pathology.—"Laboratory Investigations in the Diagnosis of Iron-deficiency and Simple Chronic Anaemia," by Dr. George Discombe.

Refresher Course Book.—The first collection of articles in the Refresher Course for General Practitioners (fully revised) are available as a book containing 55 chapters, price 25s. Copies can be obtained either direct from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1, or from booksellers.

*The logarithm of the eosinophil count is normally distributed about a mean.

Nova et Vetera

AN EXTREMELY RARE TREATISE

On February 8 there comes to auction a book so rare that only two other copies are known, one of which is in the Wellcome Museum. This is a treatise by John Banester, published in London by Thomas Orwin for Thomas Man in 1589. The full title of this bibliographical rarity is "An Antidotarie Chyrurgicall, containing great varietie of choice of all sorts of medicines that commonly fal into the Chyrurgions use: partlie taken out of Authors, olde and new, printed or written: partlie obtained by free gifte of sundrie worthie men of this Profession within this Land. By John Banester Master in Chirurgerie." This is the first edition of Banester's textbook: only one copy (not the Wellcome copy) has been exposed for auction in London during the past 50 years. In the same sale there is offered also *Epistolae Medicinales*, by Aloisius Mundelle, published in Basle about 1550.

John Banester, or Banister, was born in 1540 and began his professional life as surgeon to the forces sent to relieve Le Havre in 1563. On this expedition he met William Clowes, another surgeon, and they remained lifelong friends. For some years Banester practised at Nottingham. In 1585 he accompanied a military expedition to the Low Countries and afterwards settled in Silver Street, London. He died in 1610 and was buried in St. Olave's Church, Silver Street, but the church, with the record of his death, was destroyed in the Great Fire of 1666.

Preparations and Appliances

A CONSTANT STRENGTH TRICHLORETHYLENE INHALER UTILIZING A NEW PRINCIPLE

Dr. T. H. S. BURNS, Research Fellow, Department of Anaesthetics, Guy's Hospital, writes: The inhaler described here has been designed primarily for the production of a constant percentage of trichlorethylene vapour in air suitable for general analgesia. The proportion of trichlorethylene vapour is kept between 0.4 and 0.6% (vol./vol.) for all types of respiration likely to be met with in practice. To date, most inhalers producing vapour from a liquid drug depend on the "draw-over" principle. The output of such inhalers is obviously affected by a rise of room temperature and also by any shaking of the liquid, which will increase the surface area exposed to the air. Any draw-over machine attempting to produce a constant output must therefore incorporate a thermostat or other device to compensate for changes in room temperature. It must also include some system which will minimize the effects of shaking.

This new inhaler works on the principle of delivering a fixed amount of liquid trichlorethylene into every litre of air reaching the patient. The amount of liquid trichlorethylene necessary to produce a vapour strength of 0.5% in a litre of air is of the order of 0.02 ml. This amount is readily vaporizable at the lowest room temperature likely to be met with in practice. Thus, however much the inhaler is warmed, no more than the desired amount of trichlorethylene will be vaporized. The difficulties involved in shaking are met by a needle valve cut-out device which effectively seals off the liquid trichlorethylene in the machine as soon as it is picked up. Trichlorethylene is delivered into the air stream only when the machine is on a flat surface in its working position.

Fig. 1*a* shows a simplified cross-section of the inhaler. Compartment A is a container which holds roughly 60 ml. of trichlorethylene. The surface area of this container is large, so that the depth of the trichlorethylene is small. This minimizes any change in output due to a fall in level of the liquid. The filler (O) is arranged so that the machine is turned on its side for filling. This simplifies the prevention of overfilling (Fig. 1*b*). Compartment B is a "capacity" of about 1 litre. Its function is to assist in vaporizing the trichlorethylene and to act as a "damper" to reduce sudden changes of pressure during respiration.

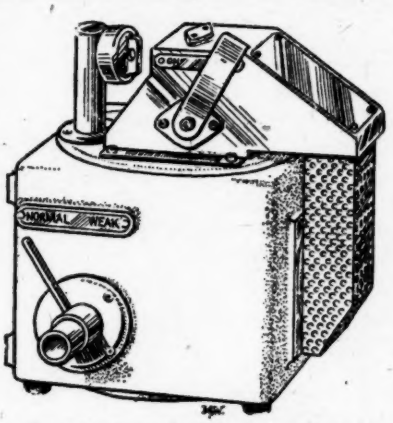


FIG. 2.—General view of the inhaler.

Air is drawn by the patient under the hood (C), through the Venturi tube (D), into the capacity (B), and on to the mask via the breathing-tube (E).

The narrowing of the Venturi tube (D) causes a reduction of pressure as air is drawn through it. A jet (F) opens into the Venturi tube at its narrowest point. This jet communicates with liquid trichlorethylene at the bottom of the container (A). This container is kept at atmospheric pressure, and so trichlorethylene tends to pass via the jet into the Venturi tube when a patient inspires. Here it is mixed with the air to form a trichlorethylene/air mixture. There is a critical air flow, below which the pressure is not reduced enough to draw any liquid into the Venturi tube. The faster the air flows the greater is the amount of liquid drawn into the air stream. The resulting mixture does not remain constant but gets richer as the air speed increases. This is shown in Fig. 3.

It should be pointed out that for a "minute volume" of, say, 20 litres the maximum air speed would be of the order of 60 litres a minute at the height of inspiration.

The inhaler is designed to give an output of between 0.4 and 0.6% trichlorethylene vapour in air (vol./vol.) for types of re-

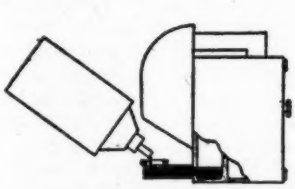


FIG. 1*b*

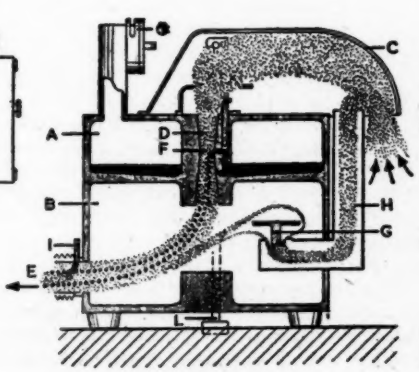


FIG. 1*a*

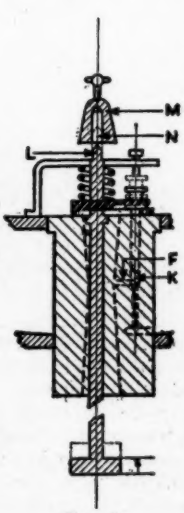


FIG. 1*c*

FIG. 1*a*.—Simplified cross-section of inhaler. FIG. 1*b*.—Filling position. FIG. 1*c*.—Safety device.

spiration varying between 7 and 20 litres a minute. These limits are marked out on Fig. 3 as a rectangle.

It will be seen that some diluting device is necessary for flow rates above 8 litres a minute in the inhaler as described so far. This dilution is accomplished by the gravity valve (G), which allows pure air to mix with the trichlorethylene/air mixture in the capacity (B). As the main mixture becomes richer, owing to the greater depression at the jet, this same depression causes the valve to admit more and more pure air, thus preventing a rise in the concentration of the final mixture. Air can be drawn through this diluting valve only via the duct (H), which takes air from the same hood as the main air stream. It is thus not possible for the diluting air stream to be blocked without blocking the air supply to the entire machine.

The valve (G) is made of a paper-based bakelite, and does not stick to its seating however moist the air becomes.

As designed, the diluting valve begins to overcompensate for the higher air flows, so that there is no danger of an extra

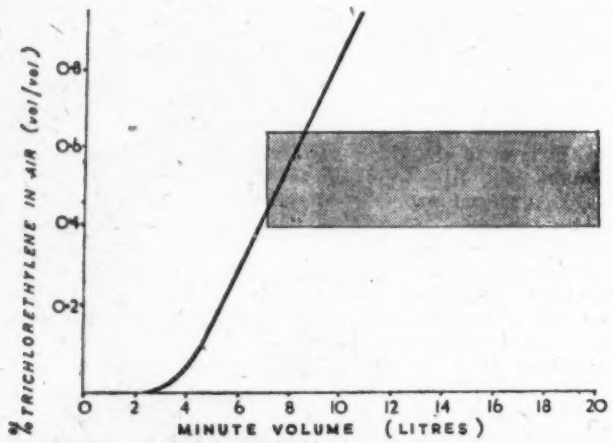


FIG. 3.—Showing that the mixture gets richer as the air speed increases.

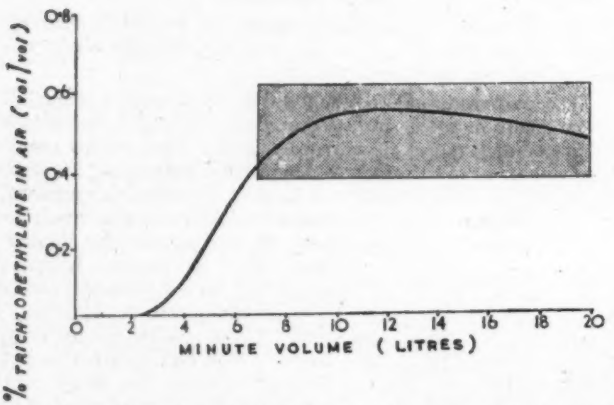


FIG. 4.—Showing the effect of the diluting valve on the output of the inhaler.

rich mixture resulting from abnormally deep inspiration. The effect of this valve on the output of the inhaler is shown in Fig. 4.

By moving a lever (I) in the delivery pipe (E) it is possible to weaken the mixture reaching the patient to about 0.35% trichlorethylene vapour in air. A useful characteristic of this weak setting device is that it produces its maximum dilution at the lower rates of air flow. For minute volumes below 8 litres the percentage of trichlorethylene vapour in air is less than 0.35%. If the minute volume rises above 16 litres the patient will receive between 0.4 and 0.5% trichlorethylene vapour in air.

In other words, should the machine be accidentally left at the "weak" setting, a mother in pain will still get an analgesic mixture on deep inspiration.

To prevent the risk of any liquid trichlorethylene being shaken into the main air stream when the inhaler is handled, a needle valve cut-out (K) is incorporated in the jet passage (Fig. 1*c*). This is operated by a push rod (L) in such a way that the trichlorethylene container is completely sealed off as soon as the inhaler is lifted up. In order to prevent the accidental or deliberate opening of this valve, when the machine is not in its working position, a bob-weight (M) is fixed above the upper end of the push rod. The push rod can open the needle valve only if it passes up inside a slot (N) in the bob-weight. It can do this only if the inhaler is stationary and horizontal. To prevent the inhaler being used by a patient while the needle valve is still closed, the "ON–OFF" indicator is arranged to show "ON" only when the valve is open.

The prototype of this inhaler was used with success on six patients at Guy's Hospital. Pain relief was superior to that obtained on these patients with gas-and-air, and all remained co-operative throughout labour. Full clinical trials are now in progress with the production models.

It is hoped to write a more detailed account of this inhaler elsewhere in the near future. So many people have willingly given their help and advice in its development that it would be impossible adequately to express my thanks to them here. However, I must mention the names of Mr. J. H. Benson and Mr. J. E. P. Dunning. Mr. Benson has been responsible for making the many prototypes and for really enthusiastic co-operation in overcoming the many difficulties which beset us in the production of the inhaler. Mr. Dunning was asked in the early stages to give his expert advice on the feasibility of the original idea, and remained to give most helpful and practical advice and encouragement right to the end. I must also acknowledge the help of the National Research Development Corporation, which has supported the development of the inhaler from the beginning; patent rights in the device are vested in the corporation, which is now considering arrangements for licensing commercial production.

Others who have helped in the development are the S.U. Carburettor Company, Zenith Carburettor Company, Imperial Chemical Industries, United Wire Works, Edinburgh, Anglo-American Vulcanized Fibre Company, Cork Manufacturing Company, British Oxygen Company, the National Physical Laboratory, and the Weyburn Engineering Company, Ltd., and to all of them I am most deeply indebted. It is again a pleasure to record my thanks to Miss Waldron, of the Department of Medical Illustration, Guy's Hospital, for the drawings.

During the epidemic of poliomyelitis in Denmark in 1952 the staff of the Blegdam Hospital became familiar with the technique of prolonged ventilation of the lungs under positive pressure, and they therefore studied the application of this system, in combination with curare, in the treatment of tetanus. In May, 1953, an opportunity presented itself for giving it a trial in the case of a 10-year-old boy admitted to hospital on the fifth incubation day. Drs. M. Björneboe, Björn Ibsen, and Steen Johnsen have reported this case in *Ugeskrift for Læger* for October 15, 1952. Curare was given by intravenous injection at short intervals for seventeen days, tracheotomy was performed, and manual ventilation under positive pressure with equal quantities of oxygen and nitrous oxide was carried out for eighteen days. Injections of pentobarbitone were also given. The authors of this report conclude: "This case will influence the future treatment of tetanus at the Blegdam Hospital, as it shows that a severe case of tetanus, hopeless according to earlier experience, may end in recovery by the help of curare and nitrous oxide narcosis in combination with tracheotomy and positive-pressure ventilation."

Correspondence

Because of the present high cost of producing the Journal, and the great pressure on our space, correspondents are asked to keep their letters short.

Treatment of Blood Disorders with A.C.T.H. and Cortisone

SIR,—A review of the effects of cortisone and A.C.T.H. in the treatment of various conditions, such as that by Professor S. J. Hartfall and his colleagues (*Journal*, January 2, p. 1), is of great interest and very welcome. Considering the importance of these substances there has been relatively little space devoted to them in the medical literature of this country, largely due to restriction of supplies and co-ordination of long-term research programmes. Restriction of supplies in this country has resulted in widespread lack of knowledge in the use of these substances. It is to be hoped that such restrictions will be considerably relaxed this year.

Like Professor Hartfall, I have given A.C.T.H. to four cases of Simmonds's disease, but found that although considerable symptomatic relief occurred this could not be maintained and hypoglycaemic episodes recurred in spite of weekly or twice-weekly injections. The Kepler and Thorn (A.C.T.H.) tests reverted to pre-treatment figures 48 hours after cessation of courses of A.C.T.H. Since changing to cortisone no further hypoglycaemic episodes have occurred. There is no doubt that control has been better and more easily maintained with oral cortisone than with intramuscular A.C.T.H., and for a period of between one and two years these patients have been very adequately maintained on 25 to 50 mg. of cortisone with sodium L-thyroxine 0.1 mg. once or twice daily by mouth. A.C.T.H. has nothing to offer over cortisone in this disease; in my own series of cases I have found replacement therapy better and easier to manage than stimulation therapy in every way.—I am, etc.,

London, S.W.1. F. DUDLEY HART.

Radiology and Lumbar Disks

SIR,—Since it is generally agreed that the onlooker sees most of the game, I trust your readers will not think it out of place for a radiologist to dare to comment under this heading. May I say that the sound sense expressed by Sir Max Page and Mr. D. W. C. Northfield (*Journal*, January 9, p. 97) seems unfortunately not too common.

Our leading neurosurgeons have urged treatment for rupture of disks, saying that they regard them as the most common cause for lumbago and sciatica, with an enthusiasm and persistence which should be surprising to members of a learned profession who ought to have a much wider knowledge of the many other contributory factors to these symptoms. It is only a few years ago that a medical faculty turned down a thesis on lumbago and sciatica for its M.Ch. on the sole basis that this was not a surgical subject. It does not seem reasonable that doctors with extensive knowledge of disease should suddenly seize on a specialists' fad and broadcast it to the public as the universal cause of a condition which has been known so long by so many. As I recorded[1]: "There is now evidence that the pendulum, having swung to its extreme limits, is settling down to much more modest excursions: that is to say, the disk is taking its place as one of the possible causes, probably because time and experience have not brought the universal successes which appeared for a period to be within the grasp of all."

It seems to have been forgotten by many that backache is one of the first indications of the effect of fatigue and toxaemia and that this should indicate the need for rest, since under these conditions sudden or prolonged strain may be permitted without the correcting influence of the muscles during normal physiological reshuffle. If rest is not provided, the disks at the sites most subject to strain will suffer and perhaps undergo degenerative changes. When I find evidence of degeneration in a disk or disks and know that I must mention it in my report I do so now with regret, since I fear that the doctor might think I too have accepted the prevailing jargon.

Severe injuries of the spine may cause damage to one or more disks, but it is not the common cause of lumbago. The most severe strains on the spine I have ever seen were those of manipulation to those patients with lumbago or sciatica while under anaesthesia. The most common causes are those strains made when the muscles are suddenly taken off their guard by some distractive influence. Thus an individual may be able to concentrate and lift a weight without harm, but if while doing so muscle control is checked by his attention being suddenly attracted elsewhere the strain is thrown on to the bones and joints, and they suffer.

No ancillary service is being abused more than radiology. Its chief abuses come from its substitution for clinical medicine. The essential contributions to sound clinical findings by myelography, radiography during distortions and contortions, and tomography are relatively few, and, provided the clinical examination is sound, fewer patients would suffer "catastrophes" by not using them than are averted by their use; and since a spectacular appearance may unfortunately be allowed to dominate the treatment. Their use has been costly in patients and their labours, in radiologists, neurosurgeons, equipment, and materials, but, as Max Page says: "The resultant form of treatment has, up to date, been productive of as much, if not more, harm than good to the community."—I am, etc.,

Birmingham, 15. JAMES F. BRAILSFORD.

REFERENCE

[1] In *Modern Trends in Radiology*, 1948, edited by J. W. McLaren. Butterworth, London.

SIR,—Dr. E. J. Crisp (*Journal*, January 23, p. 213) writes that lesions of the posterior articulations of the lumbar vertebrae give rise to pain in the leg and to "a clinical picture indistinguishable from a disk lesion." Such a statement demands at least some evidence based on anatomical or post-mortem findings. I have heard Dr. Crisp enunciate his belief before. If he persists in it, he really ought to show what are the facts supporting his thesis. I have a feeling that the scientific basis for his view is rather the same as that which inspired the Bellman to declare with such confidence in the poem describing the Hunting of the Snark:

> "Just the place for a Snark: I have said it twice
> That alone should encourage the crew.
> Just the place for a Snark: I have said it thrice.
> What I tell you three times is true."

—I am, etc.,

London, W.1. CECIL FLEMMING.

Cyclic Episodes in Hemiplegics

SIR,—I should like to call to the attention of your readers a phenomenon in connexion with hemiplegia which is important in the management of such cases. It is probably not generally known that patients suffering from hemiplegia and aphasia have recurrent episodes which may have fairly definite patterns of head noises, hypersensitivity to sound, and pain in the paralysed side. These episodes may result in irritability and bizarre actions and sometimes rage in the mind of the patient. The cause of these actions would be apt to be misinterpreted by the persons tending the patient unless the occurrence of such episodes is understood and correctly identified. These episodes are described on the basis of personal experience and subsequent verification among other patients.

The episodes may occur every few days, or every day for several days. They become less frequent as recovery progresses. The most common symptom is a heightened sensitivity to noises and head noises, sometimes associated with the rhythm of the pulse. Another common symptom is pain in the paralysed side with twitching of the muscles. There are apt to be many other, often bizarre, symptoms such as sense of vibration, irregular swings of sensations of heat and cold, anomalous taste sensations, visual aberrations, choking sensations, or fear. The episodes build up to a considerable intensity and then subside rapidly, often leaving the patient in exhaustion.

Since these episodes occur in aphasic patients, it is essential that they be recognized and understood. Misinterpretations suggesting other conditions or irascibility of the patient may result in additional discomfort to the individual.—I am, etc.,

New York. HAMILTON CAMERON.

Clot Retention

SIR,—The copy of the *Journal* containing an annotation on clot retention (October 24, 1953, p. 928) has just come to hand in this country. No mention is made of a simple method which we have been using in Auckland Hospital for several years now in practically all cases of severe clot retention which cannot be cleared by irrigation through a large whistle-tipped catheter.

The method consists simply in evacuating the clot through a special large direct vision cystoscope (approximately F 30), with the patient anaesthetized and in the lithotomy position. The instrument, by the way, is used purely and simply for evacuation of blood clot (as in clot retention) or of stone fragments. The clot can be clearly seen in the bladder when the irrigating system is turned on. The instrument is plunged into the centre of the clot, the irrigation turned off, window removed, and, with a to-and-fro shake of the shaft of the instrument, clot is easily evacuated in large quantities. The process is repeated till the bladder is empty, the operation being easier if the table is tipped with the patient in the "buttocks low" position for the final stages. A bladder full of clot can be emptied in a few minutes, and haemorrhage usually stops as soon as the bladder is empty. The method avoids an open operation and has the advantage over the Bigelow evacuator (mentioned in the annotation) that the procedure is done under vision, and one therefore knows as soon as the bladder is empty.

I was under the impression that this method was now generally adopted, and was thus surprised to find no reference to it in the annotation.—I am, etc.,

Auckland, C.1, New Zealand. L. I. PARTON.

Reaction to Blood Transfusion

SIR,—Justifiably or not, the physician must frequently bear the onus when severe or fatal transfusion reaction has occurred even though his judgment in transfusion practice is often pitted against the emotions of importunate families which in turn have drawn their impressions of transfusion benefit from television promotive campaigns by national blood-collecting agencies.

Dr. G. Discombe (*Journal*, July 5, 1953, p. 45) suggests that dextran infusion would serve as well in many cases where blood had previously been thought to be the proper infusion medium. As Dr. Discombe points out, dextran is an alternative and does have the merit of not conveying homologous serum hepatopathy, but one must not assume that this material is innocuous. All available dextrans have potential antigenicity for humans.[1] All mucinoids, synthetic as well as natural, have "blocking antibody" propensities,[2] and dextran is no exception. It is, furthermore, a sufficiently powerful "conglutinin" that 3% dextran has replaced 20% albumin in the various compatibility testing techniques where weak, incomplete, or dilute haemagglutinins are sought. Four per cent. dextran, a concentration which could be achieved in the affluent veins of a recipient, will itself act as haemagglutinin in the bloods of 20% of subjects with increased circulating glycoprotein. One per cent. dextran, an accomplished concentration in the circulating plasma of any recipient of one 500-ml. unit, will, by its presence, raise any potential anti-A titre in this recipient four-fold and any potential rhesus-type antibody titre as much as eight-fold; these figures result from actual titration of the conglutinative effect of dextran on bloods of normal subjects and of those with adaptation disease. The inference derived from these titration figures has been borne out by the conversion of a blocking-type auto-antibody in the plasma of blood dyscrasia and neoplastic disease subjects to direct haemagglutinins through dextran infusion. For this reason, reaction to plain dextran infusion (not to mention combined blood-dextran) comprising any or all the features of incompatible transfusion reactions is to be anticipated as the result if this material is extended. Likewise for this reason an *in vitro* compatibility test of the dextran to be infused with the citrated blood or unwashed erythrocyte suspensions of the prospective recipients, along the lines of ordinary "minor-side" match, should never be omitted. Some patients will then be found as unsuitable for dextran infusion as they are for blood transfusion, and we will get just as much into the habit of characterizing unsuitable recipients as we now characterize unsuitable donors, if we are careful to perform such compatibility tests on all infusion colloids.

In covert transfusion reactors, there is usually an increase in the mucoprotein component of the α and β globulin fractions of their plasma; these glycoproteins are demonstrable panhaemagglutinative "blocking" antibodies, having properties similar to the "rhesus antibodies." Some evidence is available to indicate that they arise from that depolymerization of the mucopolysaccharide (hyaluronate-like) ground substance which accompanies, that depolymerization being an accompaniment of severe decompensatory adaptation reactions.—I am, etc.,

New York. R. D. BARNARD.

REFERENCES

[1] Kabat, E. A., and Berg, D. (1953). *J. Immunol.*, **70**, 514.
[2] Barnard, R. D., and Coren, R. G. (1950). *Amer. J. dig. Dis.*, **17**, 311.

A Cosmetic Amputation

SIR,—Judged by the experience of those who serve on medical appeal tribunals, there is little doubt that the "cosmetic amputation" is now used as a routine by many surgeons, when the marginal fingers require amputation. Although in agreement with Sir Heneage Ogilvie (*Journal*, December 12, 1953, p. 1322) and Professor B. McFarland (*Journal*, January 16, p. 159) that a *mobile* intact metacarpal *with good skin cover* is of considerable functional importance to every working man's hand, it would perhaps be unwise to recommend the more distal level of amputation as a routine practice.

Hand surgery is more concerned with the primary level of finger amputation immediately following major hand injury than with what Professor B. McFarland terms "the second bite at the cherry." By implication the "second bite" condones the old teaching in the treatment of major hand injury—namely, "Save all you can at the primary operation and undertake definitive repair at a later date." There is now abundant evidence that the quality of the functional end-result following major hand injury to workpeople is conditioned by the "first bite"—that is, the primary operation. Further, very few, if any, British workmen benefit from, appreciate, or will agree to a series of hand operations.

Immediately following a major hand injury surgical planning can be definite on two matters. Its first aim is to prevent any degree of infection; secondly, a picture of the final functional end-result attainable (in a given injury) should be clearly in the surgeon's mind. To prevent infection, skin cover of the whole wound must be complete at the end of the first operation. In a working man's hand the palm should, if possible, be covered by palmar skin—no other skin in the body is capable of increasing or decreasing the thickness of its horny layer in response to functional demands, no form of skin graft can fully replace the functional quality of palmar skin. Not infrequently in major marginal finger injury, palmar cover by palmar skin is possible only after sacrifice of part or whole of the marginal metacarpal. Therefore there are some real indications for the high level of amputation even when the metacarpal bone has been left intact.

Sir Heneage Ogilvie has been quite specific in his advice and criticism, but his is quite a small bite of a very big cherry. The economic importance of hand injuries to workpeople and their cost to the community are well known. Surely the full challenge is to the organizing

ingenuity of British surgery to provide a good standard of surgical treatment of all injured hands at the acute stage. Further, in the surgery of hand injury, important surgical principles are involved which could well be taught to all undergraduates on a clinical background they would readily understand.—I am, etc.,

Birmingham, 15. WILLIAM GISSANE.

Fatal Bronchial Asthma

SIR,—I quote sentences from consecutive articles in the same *Journal*: "In the asthmatic patient with an infective sputum penicillin should be given in anticipation of bacteriological results" (Drs. C. Kelman Robertson and K. Sinclair, *Journal*, January 23, p. 187). "It is important that the acute exacerbations [of acute bronchitis] be treated energetically, with antibiotics . . . " (Mr. John Fry, p. 190).

I think these two sentences, although unfairly taken from their contexts, should be made an excuse to express a warning against the indiscriminate use of antibiotics, especially the broad spectrum variety, in chronic bronchitis and asthma. I know of one sufferer whose death was hastened by the administration of chloramphenicol which thickened the sputum until it could not be expectorated, plugged the bronchioles, and precipitated right ventricular failure. He might well have lived through another summer with more conservative treatment.—I am, etc.,

Cosham, Hants. V. H. MARTINDALE.

SIR,—The review of cases from the Edinburgh Royal Infirmary by Drs. C. Kelman Robertson and Kenneth Sinclair (*Journal*, January 23, p. 187) is of great value in recording deaths caused by an attack of asthma as opposed to those caused by secondary effects leading to pulmonary failure, etc.

To my mind, the most important finding in these cases is the 100% marked plugging of the bronchi. It is my experience as a bronchoscopist that some cases of "status asthmaticus" which fail to respond to the usual treatment can be relieved by bronchoscopic suction of gelatinous tenacious mucus, and I submit that, in this type of case, bronchoscopy is the measure which gives the patient the best chance of survival, and should always be tried.—I am, etc.,

London, W.1. A. M. ZAMORA.

The Winter Vomiting Disease

SIR,—I was extremely interested in the short article on "The Winter Vomiting Disease," by Dr. J. F. Goodall (*Journal*, January 23, p. 197). This Health Department investigated a quite extensive outbreak of infective hepatitis in the city of Exeter during 1953. This was only made possible, of course, by the willingly extended co-operation of the general practitioners practising in the city.

During the course of our investigation we were faced with the occurrence of quite a number of cases in children of general upset, nausea with or without vomiting, abdominal pain, and diarrhoea with the passage of very pale stools, but these cases showed no icterus. We formed the opinion that we were probably dealing with acute non-icteric cases of infective hepatitis, and in this opinion we were fortified by an article by Capps and Stokes in the *Journal of the American Medical Association*.[1] I am therefore interested in the grounds upon which Dr. Goodall came to the conclusion that infective hepatitis could be confidently excluded in his series of cases.

The syndrome of winter vomiting disease had a personal interest for the writer, for in the middle of a morning clinic at this time he suffered extreme nausea and sharp abdominal colic such as to cause him immediately to take up a strategic position in the small annexe to his clinic. In the event, however, he did not vomit, and by the afternoon was feeling quite well again. It is of interest that he had had a moderately severe attack of infective hepatitis in 1947. I am glad that Dr. Goodall has struck a blow at the facile diagnosis of "gastric 'flu," which satisfies the layman so easily and only confuses the epidemiologist, and congratulate him on a most useful and needed piece of research in the true Pickles tradition.—I am, etc.,

Exeter. J. H. WHITTLES.

REFERENCE

[1] *J. Amer. med. Ass.*, 1952, **149**, 557.

Death Rate in Singapore

SIR,—Some recent figures received of the crude death rates of the City of Singapore record such an improvement that I think the people in the British Isles should know of them.

In 1911 I was asked by the able Health Officer, W. R. C. Middleton, to advise what could be done to reduce the high death rate by reducing the malaria. At that time Mr. R. J. Wilkinson—later Governor of the Gold Coast—was Colonial Secretary. The population of Singapore was then roughly 280,000 between 1912 and 1919. In 1911 the peak of the death rate was 85.83. The average crude death rate from 1892 to 1911 was 42.33, and from 1912 to 1919 was 34.79. The last report for the year 1951 for the City of Singapore with a population of 747,947 was 12.73. There had been 54 cases of malaria.—I am, etc.,

Peaslake, Surrey. MALCOLM WATSON.

Training General Practitioners in Psychotherapy

SIR,—The article by Dr. Michael Balint (*Journal*, January 16, p. 115) emphasizes the deplorable state of things which we all know to exist. At least half of the cases seen by the family doctor are in need of psychotherapy, but although he may recognize that need he does not know how to respond to it. At the specialist level the psychiatrist is overwhelmed and can only deal effectively with the more advanced cases. The remedy is undoubtedly to interest and educate the general practitioner. The courses arranged by Dr. Balint for that purpose are admirable in conception and practice, but they cannot do more than influence a very small section of the medical population.

Between the wars the doctor had a much greater interest in medical psychology than he has now, and working in a large city I was able to encourage that interest by sending back full reports on the cases referred to me, and often succeeded in encouraging the practitioner to deal with a proportion of his own cases. That sort of relationship does not now appear to exist between the hospital psychiatrist and the G.P., and the natural interest of the doctor is small. The sweeping victories of biological research have given the education of the medical student a materialistic bias, just as happened in the first half of the nineteenth century when specific germs were found to be responsible for specific diseases. Medicine has to retrace its steps, and the only way to do that is to keep the psychological aspect of man and his *dis-ease* before the student throughout his whole medical course.—I am, etc.,

Scarborough. R. MACDONALD LADELL.

Medical Needs in the Gold Coast

SIR,—I would like to make a few comments on Professor Ian Fraser's letter (*Journal*, January 23, p. 214). This is a matter in which I am deeply concerned, for I am a West African recently returned to this country, after six years' work on the Gold Coast, to attempt to complete my specialist training.

Facilities on the Gold Coast are poor and conditions are very unattractive especially to doctors who have no permanent interest in the country. The climatic conditions are such that retired practitioners of advancing years are likely to suffer ill-health and be quite unable to maintain any real degree of efficiency. The short-term service, although it would introduce more highly qualified men into the Colony, does not allow for continuity of service or interest.

The solution to me is apparent. It is the provision of an adequate number of well-trained Africans, permanently domiciled in their home country, who, equipped with an intimate knowledge of local problems, and with the real

interests of their country and people at heart, can capably deal with all contingencies. The present difficulty is for these men to obtain specialized training. This cannot be obtained on the Gold Coast, and we look naturally to Britain to help in this matter. It is, however, almost impossible for an African, even though educated in England and a graduate of London University, to obtain any suitable junior post in his chosen specialty. This difficulty almost precludes the African graduate from even fulfilling the requirements for admission to the more important higher qualifications. It is little wonder that with only a handful of basically qualified practitioners the semi-literate population is easily hoodwinked by the unqualified practitioners who flourish in these territories. Unfortunately, there is no adequate legislation on the Gold Coast for dealing with these charlatans.

May I finally make a plea for the more sympathetic approach to the African seeking a suitable house appointment in this country? The Briton who is genuinely interested in the Gold Coast Medical Services can best help us by providing us the opportunity for the first-class training that British hospitals offer.—I am, etc.,

London, W.12. R. H. BANNERMAN.

The African in Industry

SIR,—I would like to thank Dr. J. H. Jackson for his bold article on the African in industry (*Journal*, January 9, p. 93). The appalling medical and social problems are not sufficiently well known, and public opinion ought to be better informed. In addition to the fearful medical needs of the miners in Southern Africa there exists an increasing moral and spiritual decline which is inevitable in such conditions. It is a burning shame that such chaos can exist in Commonwealth and colonial territories, and everything possible should be done to prevent unplanned exploitation of labour in the development of further industrial resources in these and other African territories. The co-operation of Governments and missions to alleviate and prevent this suffering is very greatly needed.

Dr. Jackson has set a good example in bringing these problems to our notice. Surely it is the duty of our profession, whether as medical missionaries or in Government service, to do so.—I am, etc.,

Cobham, Surrey. RALPH SCHRAM.

Doctors' Handwriting

SIR,—People do not as a rule boast of their lack of skill in using tools, and a man who habitually takes four putts keeps quiet about it. Parsons and actors who cannot make people hear do not boast of their inarticulate speech, but a great many people speak of their bad writing as if there was something rather clever about it. One would have thought Hamlet had exploded that idea long ago: "I once did hold it, as our statists (statesmen) do, a baseness to write fair." But it is still common for people to believe that illegible writing is a sign of "strong" or in some way desirable character, though it is hard to see how this can be.

Writing is part, and an important part, of a doctor's job. It is idle to say typewriting has superseded it; it has supplemented it—no more. Every medical practitioner carries a pen, even those who never use a stethoscope. If what you see of a man's work—his writing—is careless and slipshod, what reason have you to suppose that his diagnosis and treatment are painstaking and accurate? "Doth a fountain send forth at the same place sweet water and bitter?" There was a time when doctors did not want their patients to know what they were taking, and wrote their prescriptions illegibly on that account. But are we really to believe that every illegible N.H.S. prescription is truly and accurately dispensed? If the chemists sent every patient with an illegible prescription back to the doctor who wrote it to have it made plain, some doctors' surgeries would take about twice as long as they do now, and whose fault would that be?

One of the G.P.'s complaints against the hospitals is not only that they inform him of his patients' discharge or death about a fortnight after it has taken place (instead of the same day, which would take no longer), but that they cannot read the letter when it comes. Ideally, an examiner should plough quite ruthlessly every candidate whose writing he cannot read; but of course it should also be possible to say of him, as of Chaucer's povre Persoun, "he taughte and first he folwed it himselve."

The writer who tries to save his own time regardless of that of his correspondent is no better than the man who pushes his way first through the door and lets it slam in his neighbour's face. It would be good if some great man were to institute an annual "National Handwriting Week," but, failing that, I ask you, Sir, to lend your authority to the cause of legible handwriting.—I am, etc.,

Norwich. FREWEN MOOR.

Hospitals and the Public

SIR,—I was interested in the annotation on this subject (*Journal*, January 9, p. 89). One of the ways in which hospitals could be of much greater service to the public is by providing really adequate accommodation for relatives who have to wait for many hours while a patient is on the danger list. It does not require much imagination to realize that those hours are probably the most distressing that human beings can endure. Anything which can be done to alleviate their distress or add to their comfort at such a time should be regarded as of paramount importance. Unfortunately, in a great many hospitals the accommodation is lamentable; often not more than a draughty corridor with benches or a few hard chairs, or a depressing institution-like room, ill-lit, and without any kind of comfort. No attempt is made to make it cheerful or pleasant. I have tried to find out where the responsibility lies for the provision of such an amenity, but it seems that in many hospitals it is nobody's business. Such an amenity should surely be considered by those who have the handling of amenity funds, or alternatively it could be one of the functions of the voluntary workers who are attached to practically every hospital. It ought to be possible to have such a room properly decorated and furnished, and supplied with flowers and journals, without incurring any great expense.

I feel sure that this is just one of those things that has not been realized, and that once it has been brought to the attention of the hospital committees or voluntary workers there are many people who would be only too glad to help in this way. The pamphlet, *The Reception and Welfare of In-patients in Hospitals*, issued by the Central Health Services Council in 1953 (p. 12, para. 33, H.M.S.O., price 9d.) draws attention to this problem: "Patients who are dangerously ill may have visitors at any time, and a special problem arises when relatives have to attend the hospital for fairly long periods at irregular hours. Provision for their comfort during long waits is difficult with the present restricted accommodation, but the staff should try to ensure that they are made comfortable in accommodation as near the ward as possible during their periods of waiting. Visitors' toilet accommodation in particular is often inadequate." It should also be noted that the relatives are entirely dependent on the good will of the nursing staff for such amenities as a cup of tea or something to eat, since no provision is made for this.—I am, etc.,

London, W.9. DORIS ODLUM.

Evidence of Gout

SIR,—Dr. Oswald Savage's article on the clinical pathology (*Journal*, December 26, 1953, p. 1424) is very interesting, but the signs and symptoms of gout are so pronounced that the pathologist's aid in its diagnosis is very rarely needed.

Gout, as is known, may occur almost anywhere from tendon sheaths to the knuckles of the fingers, and as a personal sufferer, as also is my brother, I am more than interested when an attack occurs in any of my patients. In my opinion gout is due to auto-intoxication from bowel or liver or kidney: or to a combination of all three not pulling their weight and allowing absorption of excess of

uric acid into the blood stream. In some cases there is a definite cycle, an acute attack lasting 7–10 days. During this period it may clear up in one place and then attack another. A bilious attack follows with some constipation, and excretion of urine is lessened. A few days, or it may be a few weeks, free and then another attack. An attack may be, and frequently is, started by some slight traumatic injury. It occurs much more often in males, but I have in the last fortnight seen it occur in three females, all of them having passed their menopauses.

What of the cure? Is there anything that will give permanent relief? The colchicum compounds, cinchophen ("atophan"), and the like, eventually, but only temporarily, relieve the condition, but they have the disadvantages of upsetting the digestion, the bowels, and the cardiac rhythm. I have found that "leucotropin" is the least upsetting and most efficient drug, with a tablet of "veracolate" at night. A Scottish doctor friend of mine says he has permanently cured himself by taking daily a tablet of vitamin B, a couple of oranges, and a small whisky with hot water as a nightcap. Another, who used to be a great sufferer, swears by a veracolate tablet every night. A French friend of mine—in France, a wine-drinking country, the incidence of gout is very much less than in England—advises me to drink claret as a specific.

But surely the time has come for concentrated research to find a permanent cure for this most painfully distressing and disabling complaint. Could there be any link between gout, migraine, and narcolepsy—another very prevalent disease?—I am, etc.,

Norwich. P. B. CORBETT.

Ferrous Sulphate Poisoning

SIR,—In view of the letter by Mr. A. Elliot-Smith and Dr. Pamela Davies (*Journal*, January 16, p. 156) we would like to report another example of ferrous sulphate poisoning, this time a fatal one. In our department we have seen 15 cases in the last seven years, and this is the second fatal one.

A baby aged 14 months swallowed about 50 ferrous sulphate tablets three hours before admission. The child vomited soon after swallowing the tablets. In spite of gastric lavage and intravenous therapy the child died 24 hours later. Necropsy showed the stomach to be denuded of its lining, with considerable blood in the intestines. There were bilateral adrenal haemorrhages. Macroscopically, the liver looked normal.

We hope this further case will strengthen the attempts to force the hand of the manufacturers of "green, sugar-coated ferrous sulphate pills" to do something to prevent these disasters, if only to alter their fatal (literally) attractiveness to small children.—We are, etc.,

A. G. WATKINS.
P. T. BRAY.
O. P. GRAY.

Penarth, Glam.

Sterilization of Ampoules

SIR,—Your correspondents, Professor L. P. Garrod (*Journal*, December 5, 1953, p. 1269) and Dr. D. Reckless (*Journal*, January 9, p. 100), speak of the dangers of storing ampoules of solutions for spinal injections in disinfectant solution.

A considerable deal of discussion has taken place on the various ways of sterilizing these ampoules, each protagonist believing that he is describing the ideal method. Dr. Reckless believes in boiling the ampoule: Professor Macintosh[1] advocates steam sterilization: Dr. Dawkins[2] believes that the ampoules should be kept in tins in which are placed formalin tablets. ". . . Doctor and Saint, and heard great argument about it and about. . . ." May I suggest that the real question is not, "How to sterilize," but rather, "Should these ampoules be sterilized at all?"

Some time ago it was pointed out by Hewer and Garrod[3] that it is wiser to treat all ampoules with gummed labels as frankly unsterile and not to attempt to sterilize them. Since this was written it has been my almost invariable practice, and in an attempt at a modicum of standardization I have extended it to the treatment of those ampoules which have their contents etched on the glass. I believe that this procedure has certain advantages. To begin with, the ampoule is under the supervision of the anaesthetist from the moment it is taken from the maker's carton until the time he injects it. There is no risk of contamination by sterilizing fluids: the ampoule is never out of the anaesthetist's sight, and its contents are not liable to the chance (remote, I will agree) of change from boiling or steam sterilizing. The ampoule is opened by a nurse: she then holds it by the base, or puts it on a flat surface. It then behoves the anaesthetist to draw it up into his syringe without touching the neck or the sides of the ampoule. This can quite easily be done, but, should the sides be touched with the drawing-up needle, it and the ampoule should be abandoned.

Of the various ways of sterilizing the ampoule, that by steam appears to be the nearest to perfection. Nevertheless it does entail the ampoule passing out of the anaesthetist's control, and I am further disturbed by the thought that inexperienced anaesthetists may, in the absence of facilities for undertaking this, forget that it is possible and permissible to manage without any sterilization of the outside of the ampoule, and may resort to alternative methods with their consequent hazards.

May I make one point clear? I am expressing here a personal opinion based on experience of this technique and on my own thoughts: no more, no less. I make no didactic claim that steam sterilization is wrong: there should be no such statements in the light of our present knowledge of the subject. I offer an alternative for those not wholly convinced about the wisdom of attempting to sterilize ampoules.—I am, etc.,

London, S.W.15. G. C. STEEL.

REFERENCES
1 *Lumbar Puncture and Spinal Analgesia*, 1951. Livingstone, Edinburgh.
2 Personal communication, 1954.
3 *British Medical Journal*, 1942, 1, 306.

Senecio Alkaloids and Liver Cancer

SIR,—In a recent paper Hill *et al.*[1] described the occurrence of a liver disease in young children of African extraction in Jamaica. This was characterized by an enlarged sometimes tender liver, varying degrees of ascites, and hepatic cirrhosis in chronic cases. Most of the 150 children examined seemed in quite good nutritional state (particularly those who had asymptomatic liver enlargement), except a group of 11 children in which generalized oedema and other signs of what is known as "kwashiorkor" were present. In the histories of the latter children loss of appetite was recorded for 1–3 months and treatment with "bush tea" as a home remedy. Bush tea is described as an infusion of various unspecified plants, which seems to be a staple supplement of babies' diet among the Jamaican negroes of African extraction. The authors suggested that a low protein diet and possibly a toxic constituent of the bush tea may be the aetiological factors of this liver disease in children.

During the last few years we have been studying the production of primary liver carcinoma in rats by feeding different senecio alkaloids under a variety of conditions. In the course of these experiments many features described by Hill *et al.* as characteristic of "serous hepatosis," as well as those of kwashiorkor[2] have been frequently observed. These included enlarged liver with fibrosis and haemorrhage into the enlarged sinusoids, pleural and peritoneal effusion of serous fluid, and sometimes subcutaneous or generalized oedema. With larger dosage of alkaloids loss of appetite and stunted growth were seen, even though the animals received the fully adequate normal diet *ad libitum*. These features have been observed in the early stages of treatment with alkaloids of *Senecio jacoboea L.*,[3] as well as with isatidine, a senecio alkaloid from South African plants kindly supplied by Professor F. L. Warren, Department of Chemistry, University of Natal, Pietermaritzburg (the details of the latter experiments will be published elsewhere).

Senecio plants are widely distributed throughout the world, and are known to be favourite remedies of the African

negroes, who use them for a variety of disorders, including charming away bad dreams of babies (compare Watt and Breyer-Brandwijk[4] and Cook *et al.*). It is not unlikely that senecio plants are included in the bush tea or other home remedies for babies used by negroes in Jamaica, who are known to have preserved their old African customs and beliefs. Thus it is possible that senecio alkaloids are the aetiological factor of serous hepatosis and kwashiorkor in children, while malnutrition may develop as a consequence, or be a concomitant factor.

Whether the liver changes seen in children in Jamaica give rise to primary liver carcinoma in adults (as is the case in the experimental rats) is an interesting problem which requires to be investigated.—I am, etc.,

Glasgow, C.3. REGINA SCHOENTAL.

REFERENCES

1 *British Medical Journal*, 1953, 1, 117.
2 Williams, C. D. (1933). *Arch. Dis. Child.*, 8, 423.
3 Cook, J. W., Duffy, E., and Schoental, R. (1950). *Brit. J. Cancer*, 4, 405.
4 *The Medicinal and Poisonous Plants of Southern Africa*, 1932, p. 198. E. and S. Livingstone, Edinburgh.

Whither Anaesthesia?

SIR,—The letter "Whither Anaesthesia?" by Dr. C. Langton Hewer (*Journal*, January 2, p. 42) is most timely. In recent years, new drugs which have not been fully investigated have been used by people who do not possess the necessary facilities for adequate appraisal. One reason why this happens may be due to the impression, particularly amongst junior anaesthetists, that when applying for a post it is to their advantage to produce evidence of original work. When, therefore, a new drug appears, it is liable to be seized upon, tried out on a few cases, and written up as quickly as possible. The fact that a candidate for a post has written an article may impress a committee, but it does not provide evidence that he is a sound and careful anaesthetist. A safer and more efficient method of assessing the value of a new drug would be for it to be distributed to certain groups or individuals who are recognized by their colleagues as reliable investigators. Having made a thorough trial of the drug, each group should draw up a report and all information, together with any necessary warnings, should then be published.—I am, etc.,

Manchester. CHARLES E. SYKES.

Controlled Hypothermia

SIR,—The use of an antihistamine drug such as promethazine ("phenergan") seems very reasonable before a major operation, as also does the use of chlorpromazine, which reduces metabolism. Patients who have had these drugs pre-operatively come to the theatre somnolent and co-operative—rather as though they had been given a light dose of bromethol ("avertin"). Much less general anaesthesia is required and also smaller doses of relaxants. So far as my limited experience goes they certainly seem to protect the patient from shock—and in the post-operative period the patient's condition is excellent.

If a sense of proportion is maintained in the use of these drugs, I think they will take their place as useful agents in anaesthesia.—I am, etc.,

Hove. J. H. CRAWFORD.

College of General Practitioners

SIR,—While in England in 1952, I became interested in the formation of the College of General Practitioners. With the establishment of a New South Wales Regional Faculty of the College just completed, I thought a few words on the reaction of practitioners in Australia to the College might be of interest to your readers.

In this country the College has been received with widespread enthusiasm. Following the lead of New South Wales, regional faculties are now being formed in Queensland and Tasmania. In New South Wales requests for nomination forms are being received from all parts of the State. The New South Wales Faculty sent a cable to the parent body on the occasion of its first annual general meeting, and this expressed the feeling of the vast majority of practitioners here. Congratulations were offered on the successful completion of the first year of operation, and particular pleasure was expressed at the appointment as president of so distinguished a general practitioner—Dr. William Pickles.

It is felt that the activities of the College will make an important and long overdue contribution to medical education in the future, and will go a long way toward improving standards of practice.—I am, etc.,

Cessnock, N.S.W., Australia. W. A. CONOLLY.

SIR,—At the Old Bailey recently an employee of the College of General Practitioners was convicted of obtaining money from the bank by forgery. We would like it known that the College's bankers have now re-credited the College's account with the whole of the sum involved.—We are, etc.,

G. F. ABERCROMBIE,
Chairman of Council.
H. L. GLYN HUGHES,
Hon. Treasurer.
J. H. HUNT,
London, E.C.4. Hon. Secretary.

Acetone Tests on the Bed-sheets in Diabetic Coma

SIR,—In the diagnosis of possible diabetic coma in an unknown unconscious patient, it is imperative to know at once if ketones are present in the urine. If the patient is inconsiderately incontinent and no sample of urine available, as happened at King's last week, need we be balked? Indeed not. We rubbed some mixed Rothera's crystals in the wet sheet, dropped on a little strong ammonia, and a beautiful purple patch spread out and confirmed the diagnosis. Indeed, the sheet responded to the ferric chloride test with an appropriate red-wine colour. The diagnosis had been complicated by a series of confusing epileptiform fits.

This is just a little tip which may be useful some time.—I am, etc.,

London, S.E.5. R. D. LAWRENCE.

Histology of Acrosclerosis and Allied Conditions

SIR,—Acrosclerosis is of interest to dermatologist, physician, and surgeon. At a recent conference on the subject in Leeds it was felt that more information was required on the histological changes in this and in the allied conditions of Raynaud's disease and generalized scleroderma. Material is being collected for further investigation, and it would be appreciated if colleagues, medical and surgical, making biopsies of skin, gut, lung, or other tissues in this field would send some unstained sections to be added to this collection to the Dermatological Department, The General Infirmary, Leeds.—I am, etc.,

Leeds, 1. JOHN T. INGRAM.

Foreign Bodies in the Lung

SIR,—I was interested to read Dr. Bernard Laurance's account of a boy of 5 who developed a lung abscess as the result of inhaling an ear of barley (*Journal*, January 16, p. 125). In 1943 a small girl was admitted to hospital with a lung abscess. While on postural drainage she coughed up part of a spike of wild barley. Following this the symptoms completely subsided.

If any of your readers has idly placed a spike of wild barley in his mouth with the base of the seed cluster pointing towards the throat he will appreciate the mechanism of these accidents. With every movement of the tongue the barley migrates backwards at a surprising rate and becomes difficult to extract once it has reached the back of the mouth. It is easy to imagine the barley moving in this way over the back of the tongue and through the glottis. The reason for this migration is that the hairs on the barley grains are barbed and impart to the spike a unidirectional motion. It

is significant that the second of Dr. Laurance's cases had inhaled the fruit of the common agrimony. This has a ring of hooked bristles at the top.

I suggest, therefore, that there is a difference between the mode of entry of these barbed seed clusters and the inhalation of compact objects such as nuts. A nut may be drawn into the trachea by one incoordinate inspiration, whereas it seems probable that barbed seeds creep to their destination.—I am, etc.,

Bridgend, Glam. A. W. FOWLER.

Medical Museums: Information Wanted

SIR,—The Museums Association is engaged in producing a revised edition of its *Directory of Museums and Art Galleries in the British Isles*, and I shall be grateful if I may appeal through your columns for information about medical museums and teaching collections.

Only those museums and collections to which the public is admitted either freely or by special arrangement will be included in the *Directory*, and it is details of these which I am most anxious to have. It would, however, be of much use to the Association to have in its records a complete list of medical museums and medical teaching collections in the country, including those to which the public is not admitted, and details of all museums and collections would therefore be greatly appreciated. In the first instance, the information requested is limited to the name and address of each museum or collection, the title of the official in charge from whom further details could be requested if required, and whether the public is admitted.

I should be very grateful if those concerned would send this information to me at the Museums Association, Meteorological Buildings, Exhibition Road, London, S.W.7. —I am, etc.,

J. A. SIDNEY STENDALL,
Directory Editor.

The Three Hospitals Orchestra

SIR,—In June, 1952, some members of the St. Mary's Hospital Musical Society approached members of similar bodies at St. Bartholomew's and St. Thomas's Hospitals to find out if they were interested in the formation of a combined orchestra. At St. Mary's Hospital there already existed a small orchestra which had survived for just over a year, but which was gradually succumbing to the depredations which approaching examinations, increasing pressure of hospital duties, and movement of the newly qualified must inevitably impose on an orchestra recruited from a single hospital. Now well into its second year, the Three Hospitals Orchestra, under the conductorship of Mr. Norman Del Mar, can claim to be fully established, and has to its credit four public concerts, in three of which distinguished soloists have given their services.

Some of the difficulties, however, which beset the parent organization still remain, and even the combined resources of the three hospitals concerned have not always been adequate to make good the periodic loss of instrumentalists. My committee has therefore decided that the time has come to cast our net more widely, and we would now welcome players from all London hospitals (teaching and otherwise) who might be interested in the formation of a United Hospitals Orchestra. Might I, Sir, through the medium of your *Journal*, appeal for any hospital instrumentalists who would be willing to join us? The present orchestra comprises consultants, physiotherapists, housemen, nurses, and students, with the addition, from time to time, of a few professional musicians who have helped us out at rehearsals and concerts.

Any amateur orchestral player from any London hospital who would like to join us, or to obtain fuller information, should apply to: Geoffrey Spencer, Esq., Honorary Secretary, Three Hospitals Orchestra, 8, Hill Road, London, N.W.8.—I am, etc.,

HARRY L. THORNTON,
Chairman.

London, W.2.

Obituary

H. F. MOORE, M.D., D.Sc., F.R.C.P., F.R.C.P.I.

Professor H. F. Moore died at his home in Dublin on January 25, after a very short illness, at the age of 66. He was one of the leading medical men in Ireland.

Henry Francis Moore was born at Cappoquin, Co. Waterford, where his father was an engineer engaged in railway construction. He studied in University College, Dublin, where he graduated in medicine, with first-class honours and first place, in 1912. After serving as a house-surgeon in the Mater Misericordiae Hospital he was awarded a travelling studentship and proceeded to Germany in 1913. The outbreak of the 1914 war forced him to return home after about a year. This proved to be a decisive point in his life. He went to the Rockefeller Institute for Medical Research in New York, working there for four years. At this time researches were being conducted into the value of inorganic copper compounds in pneumonia. He was for some time engaged in this work, on which he published his first papers. During this time he made personal contacts and friendships which he maintained throughout his life, and he married Miss Frances L. Thomas, who was his constant support and companion until her death early last summer.

Admitted M.D. in 1917, he was appointed to the staff of the Mater Misericordiae Hospital on his return to Dublin. Academic and other honours came quickly. In 1922 the degree of D.Sc. of the National University of Ireland was conferred on him for his published work. He obtained the M.R.C.P.I. in 1930, and was elected F.R.C.P.I. in 1932. From 1932 to 1934 he was president of the Section of Medicine of the Royal Academy of Medicine in Ireland, and in 1933 and again in 1952 he was president of the Section of Medicine when the British Medical Association held its Annual Meeting in Dublin. In 1938 he became M.R.C.P. and was elected F.R.C.P. in the following year. He was a member of the Medical Registration Council of Ireland and of the Medical Research Council of Ireland, in each case from the foundation of these bodies. In 1927 he was appointed professor of medicine in University College, Dublin, and occupied the chair until his death.

We are much indebted to Dr. EDWARD T. FREEMAN for the following appreciation: Henry Moore returned to Dublin at a very favourable moment. His careful laboratory training in New York and the scientific approach to problems which he had witnessed and taken part in equipped him to be the forerunner in the introduction of these methods to Irish medicine. In the Mater Misericordiae Hospital he was instrumental in setting up and equipping a biochemical laboratory long before such a department was operating in any medical school in Ireland. He was also in the very beginning of electrocardiography and in the treatment of diabetes by insulin, and of the investigation of thyrotoxicosis by observation on the basal metabolic rate. Henry Moore made many contributions to medical journals —to the *Journal of Experimental Medicine*, to the *British Medical Journal*, to the *Quarterly Journal of Medicine*, the *Lancet*, the *Irish Journal of Medical Science*, and others. Two years ago, through his influence, the firm of Merck placed at the disposal of the Medical Research Council of Ireland a supply of cortisone valued at over £10,000, for the purpose of research. Already suffering from hypertension and knowing the need to go more slowly, he threw himself into this activity with all the enthusiasm of his youth. He

was appointed chairman of the committee set up by the Council to administer the supply of the drug and to collect and to relate the results of treatment. He abandoned much of his private practice, incurred much resentment and hostility through his refusals to supply cortisone where the indications did not warrant it, and seriously undermined his health in carrying out this task.

In the autumn of 1952 he was invited to lecture in the U.S.A. on the results obtained by his collaborators and himself. He found the strain of the American tour very heavy and had to come home before his programme was completed. His last year was a gallant struggle against gradually failing powers. The unexpected death of his wife last summer removed his constant prop, and a series of minor cerebral episodes was mercifully terminated by a cerebral haemorrhage from which he did not awaken.

Henry Moore left an indelible mark on Dublin medicine. He flowed in on the wave of biochemistry and mechanization which in the early nineteen-twenties overwhelmed bedside observation. He was not gifted with deep insight, but he had an uncanny sense of seeing the essential and of seizing it. His mind therefore led him on one track, and he pursued this in the face of every obstacle. This search of the moment dominated all his actions, all his thoughts, all his conversation. One can see him, his short figure approaching with quick steps, his eyes glinting, and his finger raised: "I heard from X this morning. It is all right about Y on Tuesday." With an effort one pulled oneself together to remember who or what X and Y were. This canalized interest made him a poor committee man. He had no feeling for business or "affairs," and at times his complete disregard for agreed decisions was a source of embarrassment to his colleagues.

In his earlier years he prepared his clinical lectures and ward rounds with scrupulous attention to detail, but he never knew a student, and few of them knew him. He was as aloof to them as they were remote from him. But if any of them or of their friends were ill or in trouble they were amazed to find that the indifferent mask concealed kindness and understanding beyond anything that they had ever suspected. To really know him one should have seen him in his beautiful home in Killiney, where his wife, so perfect a hostess, joined with him in making welcome the appointed guest or the casual wayfarer. This lovely home was part of him, and the wrench of leaving it after his wife's death tore him apart.

No character is really simple to break down, and no complex person had more different facets than Henry Moore. In spite of occasional exasperation, his colleagues and professional brethren all held him in high regard, and very many of them in real affection.

H. E. GIBBS, M.D., F.R.C.S.Ed.

We record with regret the death of Dr. H. E. Gibbs, a Vice-President of the British Medical Association, at his home at Wellington, New Zealand, on December 23, 1953, at the age of 80.

Harry Edward Gibbs was born in London, and when he was only 4 years old his father died. His mother thereupon emigrated to New Zealand with her large and young family, and he and his brothers grew up to play a prominent part in the development of professional life in the Dominion. After leaving Nelson College in the South Island—where he had a distinguished scholastic and athletic record, being captain of both the cricket and Rugby teams—he came back to Britain to study medicine at Edinburgh University. He graduated M.B., Ch.B. in 1898, took the F.R.C.S.Ed. two years later, and proceeded to the M.D. in 1901. After graduation he held house appointments at Edinburgh Royal Infirmary and later at Liverpool. When he returned to New Zealand he first went into practice at Hawera, in the province of Taranaki, but in 1901 he moved to Wellington, where for the next 50 years he practised from his home in Willis Street. In the early years of this century, while the capital city of New Zealand was rapidly expanding, he built up a large general and surgical practice, and in 1902 he was appointed surgeon to the Wellington Public Hospital.

Dr. Gibbs had a firm belief in the importance of a strong professional organization, and for many years was prominent in the affairs of the New Zealand Branch of the B.M.A. As honorary general secretary of the Branch from 1907 to 1923 he laid the foundation of the divisional organization which served the profession so well in the difficult later years of a newly introduced national health scheme. He was also chairman of the Branch council in 1926 and 1927. When the parent Association held its Annual Meeting at Portsmouth in 1923, Dr. Gibbs, who attended as the representative of the New Zealand Branch, was rewarded for his services to the profession in his adopted country by being elected a Vice-president of the B.M.A. He had been prominently concerned in the promotion of a medical defence scheme and of the New Zealand Medical Benevolent Fund, and was regarded as the outstanding figure in medical organization in that country. He remained an officer of the Fund until his death. For the last few years of his life he was an honorary member of the New Zealand Branch by virtue of his 50 years' membership: as long ago as 1927 the Branch recognized his outstanding services by presenting him with a gold watch and chain.

A man of wide interests, all pursued with vigour, Dr. Gibbs was largely responsible for the development of the King George V Memorial Health Camps, and he took an active part in the management of the institutions until his death. He had long been recognized in New Zealand as one of the old school of medical practitioners—guide, philosopher, and friend to his patients, with a deep sense of personal responsibility and a keen interest in the prestige of the profession.

Dr. Gibbs's wife, formerly Miss Annie M. W. Gardner, of Edinburgh, died in 1945. They had a daughter, now Mrs. Margaret Lawton, of Southern Rhodesia, and two sons, Dr. J. G. Gibbs and Dr. E. G. Gibbs, a surgeon in Wellington. Two of his brothers also survive him—Dr. S. A. Gibbs, of Nelson, who, too, has played a prominent part in New Zealand medicine, and Dr. J. H. Gibbs, who practised in Edinburgh for many years, but who has now retired to live in the North Island of New Zealand.

W. H. WOOD, M.D.

Professor W. H. Wood died at his home in Aberdaron, Caernarvonshire, on January 21 at the age of 66, five years after retiring from the Derby Chair of Anatomy in the University of Liverpool, to which he was appointed in 1925.

William Henry Wood was born on April 11, 1888, and received his early education at Lymm Grammar School, where he displayed an aptitude for the physical sciences and a precocious skill at both cricket and Association football, playing, even as a boy, for well-known adult clubs. His entry into the Victoria University of Manchester was, at least in part, in pursuit of opportunities to further his athletic interests, and, choosing the faculty of science, he graduated B.Sc. in 1908, with physiology as his principal subject. During his course he attracted the attention of the late Sir William Stirling, who offered him a staff appointment in the department of physiology, which he held for three years. The interest thus developed led naturally

to medicine, in which faculty he enrolled, graduating M.B., Ch.B. in 1913. War broke out in the following year, and Wood was one of the first to enlist, serving in the R.A.M.C. in France during the early stages, whence he was transferred first to Mesopotamia and later to India.

On his return to Manchester at the end of the war a chance meeting with the late Sir Grafton Elliot Smith, then professor of anatomy at Manchester, led to an invitation to join the brilliant staff he had collected, and it was as a member of this team of teachers and research workers that Wood developed his exceptional and powerful methods of teaching which were the basis of his success at Liverpool. In 1923 he was awarded a gold medal for his thesis for the degree of M.D. It is a disappointment to many that his views concerning the anatomy, and particularly the actions of the small muscles of the hand and foot, now enshrined in orthopaedic practice, have not been separately published.

Throughout his teaching career Wood was governed by the deep conviction that the profession of medicine, which had developed anatomy as a discipline separate from generalized biology, was the proper recipient of the anatomist's services, and that the student himself was the natural point of contact. Accordingly the student had his first care. His reward was certain, alike in the satisfaction with which he watched their successes and in the deep attachment which many generations of students retained for a beloved master whose last years of office were clouded by physical infirmity. In Wood's hands Liverpool became a great teaching school. From 1933 to 1939 he conjoined the arduous duties of a departmental headship with a highly successful deanship of the faculty of medicine.—T. J.

Mr. DAVID LIGAT, consulting surgeon to the Buchanan Hospital, St. Leonards-on-Sea, and to the Bexhill Hospital, died on January 14 at the age of 80. Born near Glasgow on September 18, 1873, he passed the final M.B., C.M. examination at Glasgow University in 1894 before he was 21. Shortly afterwards he took an appointment as a ship surgeon and acquired a love of the sea and ships which he never lost. He then lived at Manchester, where he took the D.P.H. in 1898, and for a time held an appointment in the public health service. Later he moved to London, and was in practice in the Commercial Road for some years until 1909, when he moved to Hastings. A few years later he finally settled in the neighbouring town of St. Leonards, at the same time setting up his plate as a consulting surgeon in Devonshire Street, London. Earlier, in 1907, he had obtained the diploma of F.R.C.S. Mr. Ligat held a number of appointments at the Middlesex Hospital, including that of acting assistant surgeon from 1915 to 1919, and became surgical clinical assistant at the Evelina Hospital for Sick Children just before the first world war. In 1919 he delivered a Hunterian Lecture before the Royal College of Surgeons on the significance and surgical value of certain abdominal reflexes. His name will be perpetuated in "Ligat's test," which is still of great service in the diagnosis of appendicitis. During the first world war he operated on many of the casualties admitted to hospitals in Hastings and St. Leonards. In 1922 he joined the surgical staff of the Buchanan Hospital, and there he did brilliant work for many years, being particularly successful in abdominal surgery. In the last war he also operated at the Royal East Sussex Hospital, Hastings. In January, 1944, he lost his right arm in an air raid, and, although he made a good recovery, was henceforth denied his three great interests in life—surgery, golf, and playing the violoncello. Mr. Ligat was an active member of the British Medical Association, being chairman of the Hastings Division in 1922–3 and president of the Sussex Branch in 1924–5. For some months in 1949 he served as honorary secretary and treasurer of the Division, whose meetings he continued to attend up to his 80th year. His innumerable patients will always be grateful for his unfailing kindness, and his many friends will remember above all his fearlessness, his forthrightness, and his courage in adversity during the last years of his life. We extend our deep sympathy to his widow and daughter.—W. E. P. and A. F. W. H.

Dr. MARGARET M. OWEN died on January 19, after a long illness, at the age of 61. Her fortitude was an inspiration and example to all. Margaret Mercedes Morton, who was born on August 7, 1892, lived in Spain in her early years, but about 1912 she went to live with relatives in Glasgow and to study medicine at the university, from which she graduated M.B., Ch.B. in 1917. After holding hospital appointments in London, she joined the school medical service in Sheffield in 1920, an appointment she relinquished when she married in 1923. Her active interest in medical practice was renewed when she became medical officer to the Sheffield branch of the National Birth Control Association in 1934. At first she worked on a voluntary basis, but very soon afterwards she became medical officer to birth control clinics under the West Riding County Council. The organization and development of the service in the Sheffield area was largely due to Dr. Owen's enthusiasm. Her quiet and constant application of certain principles, which she believed were the right of every woman, resulted in great improvements in the physical and mental well-being of many of her patients. In addition, she was always willing to train students and practitioners in her methods. For many years Dr. Owen held office in the Sheffield Association of the Medical Women's Federation, being its president from 1951 to 1953. She will be greatly missed by her colleagues and patients.—D. P.

Medical Notes in Parliament

PREVENTIVE MEDICINE AND LIBERTY OF SUBJECT

LORD DOUGLAS OF BARLOCH initiated a debate in the House of Lords on January 27 on what he called mass medication. He complained of the infringement of the liberty of the subject, and the danger to the health of individuals, inherent in projects of mass medication such as the addition of chalk to flour, iodine to salt, and fluorine to public water supplies. The history of all these projects, and the pros and cons—with emphasis on the "cons"—he developed in detail. His basic theme was that the passion to regulate the lives of others was deep-seated and hard to root out, and was most dangerous and most insidious when it arose not from motives of personal gain but from the desire to inflict benefit on others. His criticism of mass medication was that it offended against the basic code of medical practice. The dose was administered without any examination of the patient, without regard to age or sex or physical condition, and irrespective of whether it was required or not. It was, he asserted, reckless, unethical, and an invasion of the liberty of the subject which ought not to be tolerated.

LORD AMULREE, denying that there was any negation of medical practice, said that Lord Douglas took a wrong view of what a doctor was for. A doctor did not exist primarily to cure his patients but to stop them from becoming sick. If by the adoption of simple measures a certain amount of disease could be prevented, that was not only doing good for the community but carrying out an economic work as well. Chlorination of water did no harm whatever. The same applied to the addition of chalk to bread. Various complaints arising from an insufficiency of calcium were preventable by the addition of chalk to flour. Similarly, if goitre could be prevented by the addition of small and controlled quantities of iodine to salt, he could see no objection to it. In either case flour and salt to which there had been no addition could be bought.

The question of putting fluorine into water was a much more difficult one. A great deal of work had been done in the United States which showed that apparently it stopped dental caries. He thought that it was not entirely proved, and he felt sure that if the Government embarked on an experiment they would merely raise the total quantity to one part in a million—which already existed in many of the water supplies in this country. As people had been drinking water with one part of fluorine per million ever since water was first drunk, with no great trouble, he could see no particular danger in that.

The New Truth

LORD WEBB-JOHNSON said that the attitude of the medical profession towards disease had changed radically in the past century. They were no longer agents for the recognition and treatment of disease, but pioneers in the effort to prevent it. The new truth was often opposed by a fixed opinion or by a bias, and it was necessary to find out whether the opposition was based on scientific principles or arose from total conservatism.

Iodine was an essential to the healthy functioning of the thyroid gland. Fifty years ago, when he saw Kocher operating on goitres in Switzerland, there was no idea how its incidence could be prevented or diminished. Thirty years ago, in Cleveland, Ohio, he saw George Crile operate on 20 goitres in a morning. Crile's whole object was to find out why the people were getting goitres, and how to prevent it. Last week Crile's son was over here, and told him that now in Cleveland he operated on possibly one or two goitres a day, and some days none. Lord Webb-Johnson asked, "Is it because you have iodized salt?" The reply was, "It may be, but we do not dismiss other possible factors. For instance, in Cleveland to-day half the vegetables eaten are grown outside the area, which is an area of endemic goitre. They are grown in the West, where the soil is saturated with iodine, and they get their iodine through canned vegetables." These things righted themselves, but that was no reason for condemning the pioneer who first proved that a disease was due to a deficiency of iodine and urged that artificial means should be used to meet the deficiency.

He protested against the suggestion that "mass medication" was contrary to the ethics and traditions of the medical profession. The proposal Lord Douglas had criticized was not mass medication; it was a reinforcement of Nature's supply in a particular district. He objected to Lord Douglas's remarks about "adding drugs to the water supply." All that was being suggested, if it was actually being suggested as a practical proposition at the moment, was the addition in that particular district of something in which Nature had been deficient. There was no limit to which the opponents of sanitary measures would go. From cancer downwards the whole gamut were paraded as dangers.

Government Reply

LORD CARRINGTON, Parliamentary Secretary to the Ministry of Agriculture, replying for the Government, recalled the recommendation of the B.M.A. Committee on Nutrition that the consumption of calcium should reach 0.8 g. per adult per day, and the report of the National Food Survey that in the first half of 1952 the national average intake would have been about 10% below this had it not been for the addition of calcium to flour. The addition did no harm to anyone, and there was a permitted exception for 100% extraction wholemeal flour.

A special committee of the Medical Research Council on Thyroid Diseases reported in 1948 that goitre appeared to be on the increase, and recommended that preventive action on a national scale should be taken by the addition of a trace of iodine to domestic salt. The recommendation was endorsed by the committee on medical and nutritional problems of the Ministry of Health, and was referred to the Food Standards Committee of the Ministry of Food for investigation of the technical problems. These had not been fully solved. The committee recommended favourably in March, 1950. Representations were received from a large number of people, including the medical profession, the trade, medical authorities, and others. These were considered by the Health Departments and the committee, but the committee had not yet made its final report. In a number of countries where goitre was common salt had been iodized for a number of years, and nowhere had there been any resulting harm; in fact, the experience had been that nothing but good had resulted.

On the fluoridation of water supplies, as this was the only measure which so far gave any promise of preventing or reducing the incidence of bad teeth, the Minister of Health had announced on December 3, 1953, acceptance of the recommendation of the medical mission that had visited the U.S.A.[1] There were many areas in Britain where there was already enough fluorine in the water supply, and where no more would be added. There was no scientific basis for the allegation that fluorides in quantities of 1.0 to 1.5 parts in a million had any harmful effect; but there had been some confusion with industrial fluorosis, which was the result of a heavy concentration of fluorides in the atmosphere in the form of dust.

The last question was that, even assuming these measures were medically justified, they should be withheld on the ground that they infringed the liberty of the subject. A balance could be struck only by going fully into each proposal. He agreed that medical justification was not of itself sufficient. Political and philosophical implications must be considered. Nowadays it was believed that Governments had a general responsibility for ensuring the health of the people. When an overwhelming case had been made on scientific grounds, and they were convinced that what was recommended was practical and could not possibly result in anything but good to the public health, then they must consider taking action of the kind that had been described as mass medication. They would be failing in their duty if they did not take into account the great benefit to the public health that would result.

Hearing-aids

MR. IAIN MACLEOD informed Dr. BARNET STROSS on January 21 that the proportion of bone-conduction hearing-aids required, compared with air-conduction models, was estimated at less than 5%. About 7,000 people had been supplied with them in the 12 months since they became available, and supplies were ample. Within a month or two there would be no waiting-list.

Acidity in Soft Drinks

Dr. BARNET STROSS asked the Minister of Food to state the measure of acidity in the mineral drink "Cola" in terms of the hydrogen ion concentration, and what other substances it contained besides caffeine, phosphoric acid, sugar, and water. Dr. CHARLES HILL, the Parliamentary Secretary, told him on January 25 that the *p*H of Cola drinks sold in the U.S.A. was 2.6, though a sample taken in this country was slightly less acid. He had no information about the ingredients.

Dr. STROSS said the answer showed that the drink was as acid as vinegar even if it were masked by the sugar content. Evidence was given before a U.S. Congress committee in 1950 about the danger of this drink in relation to dental nutrition, in that it caused teeth erosion. He asked the Ministry to check these facts through the Medical Research Council. Dr. HILL replied that the level of acidity was only slightly more than that for soft drinks containing acid generally. The Committee on Food Standards would soon, it was hoped, consider the position generally, including the question of acidity.

Powdered Milk Code

Lieutenant-Colonel M. LIPTON asked the Minister of Food on January 25 what further investigations had been made to prevent a recurrence of food-poisoning in schools as a result of using powdered milk. Dr. CHARLES HILL, Parliamentary

[1] See *British Medical Journal*, July 11, 1953, p. 88.

Secretary, replied that there had been comprehensive bacteriological tests of the milk powder which caused the recent outbreaks, and the conditions and production at the particular factory had been thoroughly investigated. As a result a code of practice for the manufacture of dried milk was being prepared, and this would be issued to all manufacturers soon.

In the House of Lords on January 26, LORD AMULREE introduced the Abortion Bill, and it was read a first time.

Medico-Legal

DOCTOR A "PUBLIC AUTHORITY"

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

Although there is no time limit for the institution of criminal proceedings, civil actions of all kinds have to be brought within certain fixed time limits, which vary with the type of action. This is plainly necessary so that there is some end to disputes and so that they can be decided before the evidence on which alone they can be decided has vanished. "Interest rei publicae ut fit finis litium." The periods of limitation are now set out in the Limitation Act, 1939, except in the case of actions against some of the public corporations which run the nationalized industries, for which special periods of limitation are provided in their own nationalizing statutes; and there exist certain other special periods. For ordinary actions for damages for breach of contract or for torts, the period is six years. But when the action is brought against a public authority the period within which it must be brought is one year only. "Public authority" is not defined in the 1939 Act, but bears the same meaning as it did under the Public Authorities Protection Act, 1893, which provided a limitation period of six months. Any person who is sued for any act done or for any neglect or default in doing an act, "in pursuance or execution or intended execution of any Act of Parliament, or of any public duty or authority," is a public authority within the meaning of the statute. Nice questions can arise whether or not a particular person or body falls within this definition on any given occasion.

On January 29 Mr. Justice Pilcher,[1] in the Queen's Bench Division of the High Court, decided that a doctor, who as part-time specialist in charge of the physical medicine department of a hospital was acting in the execution or intended execution of a duty imposed by the National Health Service Act, 1946, was a "public authority." Accordingly he dismissed an action for negligence brought against the doctor by a patient because the writ had been issued more than a year after the cause of action—that is, the alleged negligence of the doctor and the damage resulting from it—had first arisen. A private Member's Bill seeking to make all periods of limitation three years was recently introduced into the House of Commons with the support of the Government.

[1] *The Times*, January 30.

The Services

The *London Gazette* has announced the following awards:

Bar to Air Force Cross.—Wing Commander H. H. S. Brown, A.F.C., R.A.F.

Air Force Cross.—Group Captain D. A. Wilson and Wing Commander G. H. Dhenin, G.M., R.A.F. Surgeon Lieutenant-Commander W. H. B. Ellis, R.N.

Surgeon Rear Admiral R. C. May, O.B.E., M.C., R.N., has been appointed Honorary Surgeon to the Queen in succession to Surgeon Rear Admiral T. Madill, C.B., O.B.E., R.N.

The announcements in the *London Gazette* dated October 30, 1953, and in the *Journal* of November 28, 1953 (p. 1227), concerning the award by the President of the U.S.A. of the decoration of Legion of Merit, Degree of Legionnaire, to Colonel G. Anderton, O.B.E., late R.A.M.C. (now R.A.R.O.), in recognition of gallant and distinguished services during the operations by the United Nations in Korea, should have read Legion of Merit, Degree of Officer.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending January 16 (No. 2) and corresponding week 1953.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1954					1953				
	Eng. & Wales	Lond	Scot	N. Ire	Eire	Eng. & Wales	Lond	Scot	N. Ire	Eire
Diphtheria	21	1	6	0	2	12	1	9	0	2
Dysentery	378	81	147	33	6	312	19	96		3
Encephalitis, acute	3	1	0	0		8	1	0	0	
Enteric fever:										
Typhoid	4	0	1	1		1	0	0	0	1
Paratyphoid	4	1	0	0		8	1	1 (B)	0	0
Food-poisoning	110	12		1		46	0		3	
Infective enteritis or diarrhoea under 2 years				7	10				11	16
Measles*	1,150	18	29	14	160	21,383	1777	319	46	114
Meningococcal infection	36	6	13	4		45	5	30		2
Ophthalmia neonatorum	26	1	3	0		40	2	15	1	
Pneumonia†	963	58	329	14	3	1,204	66	333	32	
Poliomyelitis, acute:										
Paralytic	27	1	1	4	4	25	0	3	1	5
Non-paralytic	13	0				6	0			
Puerperal fever§	250	28	11	1	1	212	24	15	3	1
Scarlet fever	915	36	207	44	37	1,589	65	332	44	55
Tuberculosis:										
Respiratory	744	90	144	30				128	26	
Non-respiratory	113	7	20	4				30	6	
Whooping-cough	2,366	97	419	75	93	2,160	99	192	53	80

DEATHS in Great Towns	1954					1953				
	Eng. & Wales	Lond	Scot	N. Ire	Eire	Eng. & Wales	Lond	Scot	N. Ire	Eire
Diphtheria	0	0	0	0	0	0	0	0	0	0
Dysentery	0	0		0		0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	10	1	4	2	1	13	3	2	0	1
Influenza	42	4	1	1	0	72	14	2	1	0
Measles		0	0	0	1		0	0	0	0
Meningococcal infection		1	1				1	1		
Pneumonia	432	51	30	14	9	491	87	36	14	11
Poliomyelitis, acute	6	0			0	2	0			0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	139	15	23	4	10	182	32	17	4	12
Non-respiratory		2	3	0	1		1	3	0	0
Whooping-cough	2	0	0	0	0	0	0	0	0	1
Deaths 0–1 year	272	33	27	10	23	293	34	41	9	14
Deaths (excluding stillbirths)	7,079	953	754	133	221	7,697	1300	773	149	207
LIVE BIRTHS	7,696	1146	879	231	392	7,548	1113	965	264	419
STILLBIRTHS	218	24	38			180	24	25		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Vital Statistics

Industrial Accidents and Diseases

The number of workpeople (other than seamen) in the United Kingdom whose deaths from accidents in the course of their employment were reported in December, 1953, was 116, compared with 125 (revised figure) in the previous month and 137 in December, 1952.

The number of cases of industrial diseases in the United Kingdom reported during December was as follows: lead-poisoning, 11; other poisoning, 2; anthrax, 3; epitheliomatous ulceration, 11; and chrome ulceration, 10; total, 37. There were no deaths.—*Ministry of Labour Gazette*, January, 1954.

Scotland in 1952

The infant mortality rate of 35.2 per 1,000 live births was lower than any previously recorded in Scotland. The general death rate of 12.03 per 1,000 population was lower than any previous rate, except for 1948, when it was 11.0. The still-birth rate continued to fall, being 26.2 per 1,000 total births. The ratio of boys to girls born was 1,048, much lower than the average of 1,063 for the years 1946–51. The birth rate was 17.68 per 1,000 population, slightly less than in 1951, and much the same as in 1937–8. These figures appear in the *Ninety-Eighth Annual Report of the Registrar-General for Scotland, 1952* (H.M.S.O., 10s. 6d.).

A comparison of standardized death rates in Scotland and in England and Wales shows the following death rates per million, those for England and Wales being in parentheses: tuberculosis of respiratory system, 282 (211); malignant neoplasms 2,126 (1,979); diabetes mellitus, 103 (75); vascular lesions affecting C.N.S. 1,936 (1,564); heart diseases, 4,104 (3,366); hypertensive disease, 367 (428); pneumonia, 402 (442); and nephritis and nephrosis 117 (133)

Week Ending January 23

The notifications of infectious diseases in England and Wales during the week included scarlet fever 1,138, whooping-cough 2,357, diphtheria 18, measles 1,106, dysentery 490, acute poliomyelitis 37, paratyphoid fever 4, and typhoid fever 3.

Infectious Diseases

A rise occurred in the incidence of infectious diseases in England and Wales during the week ending January 16. The largest increases in the number of notifications were 210 for whooping-cough, from 2,156 to 2,366, 123 for scarlet fever, from 792 to 915, and 56 for dysentery, from 322 to 378

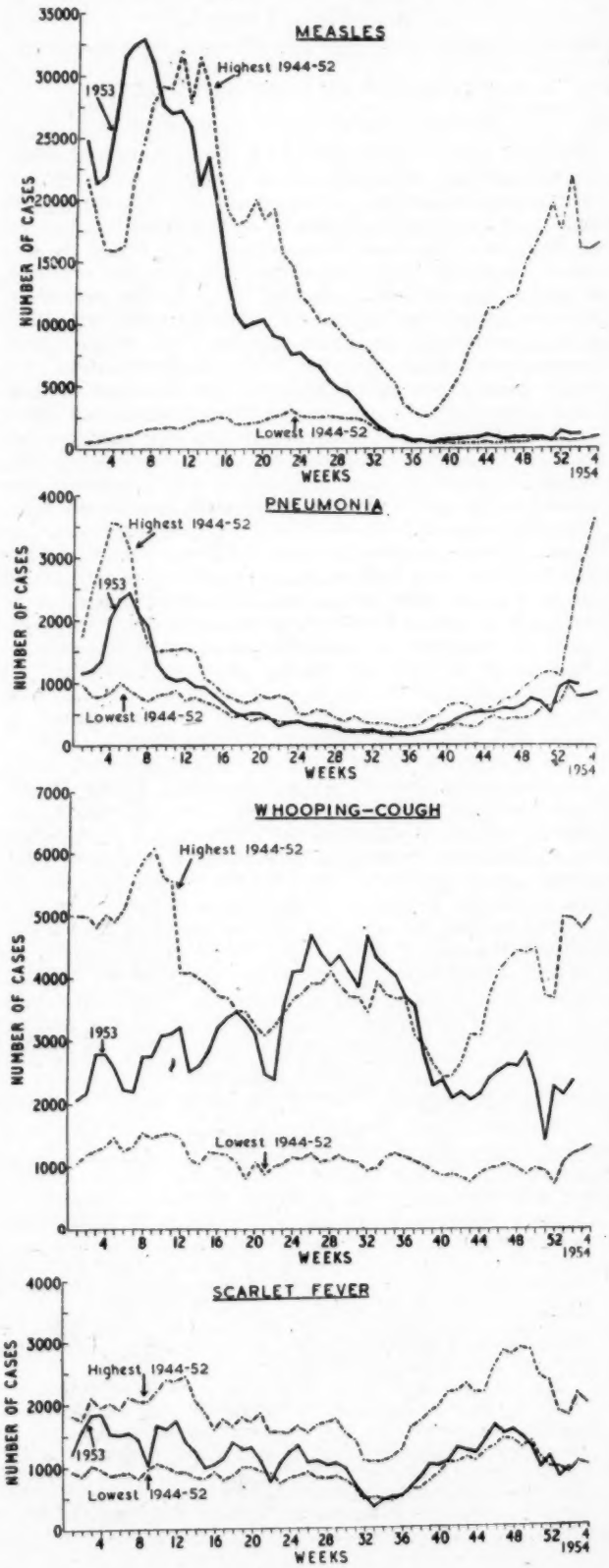
The only large variations in the local trends of whooping-cough were increases of 57 in Staffordshire, from 78 to 135, and 55 in Warwickshire, from 132 to 187. A small rise in the incidence of scarlet fever occurred in every region, but no large fluctuations were recorded. 1,150 cases of measles were notified, being 16 more than in the preceding week. The only fluctuations of any size in the local trends of measles were an increase of 64 in Staffordshire, from 140 to 204, and a decrease of 40 in Lancashire, from 346 to 306. 21 cases of diphtheria, the same number as in the preceding week, were notified. The chief feature of the returns of diphtheria was a rise in Lancashire, from 2 to 7, 5 of the cases being notified in Liverpool C.B.

40 cases of acute poliomyelitis were notified. These were 8 fewer for paralytic and 4 more for non-paralytic cases than in the preceding week. The largest returns were Gloucestershire 6 (Mangotsfield U.D. 3), Suffolk 4, Essex 3, Lancashire 3, and Yorkshire West Riding 3.

The increase in the incidence of dysentery was mainly contributed by Yorkshire West Riding, where a rise of 35 was recorded. The largest returns were Yorkshire West Riding 83 (Leeds C.B. 45, Bradford C.B. 17), London 81 (Islington 36), Lancashire 40 (Bolton C.B. 23), Middlesex 33, and Norfolk 20 (Norwich C.B. 20).

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the nine years 1944–52 are shown thus - - - - - - - - -, the figures for 1953–4 thus ————. Except for the curves showing notifications in 1953–4, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.



Medical News

Professor H. A. Krebs, F.R.S.—The Friends of the Hebrew University of Jerusalem gave a dinner on January 27 to celebrate the award to Professor H. A. Krebs of the Nobel prize in medicine for 1953. Sir Henry Cohen, who was in the chair, said that really this dinner had its origin 125 years ago, when Wöhler synthesized urea. This was really the beginning of examination by the chemist of living matter. The chair of biochemistry was established in Liverpool in 1903, and Sheffield had followed suit 40 years later when it appointed Professor Krebs professor of biochemistry. There had been many great figures in the history of medicine and science who had been recommended for the Nobel prize, but only a few of them had been chosen. At the same time Professor Krebs had been awarded the Lasker prize of the American Public Health Service, a recognition of the significance of his work to medicine. Tributes to Professor Krebs were then paid by the Ambassador of Israel and by Sir Ben Lockspeiser. In reply he said that what was not rare was certainly his "dose of talent." He had had quite unusual opportunities for doing the work which had led up to the award of the Nobel prize. After qualification he had had the chance of working on a whole-time basis; then he was associated with Otto Warburg and later with Gowland Hopkins. His great advantage had been that he had had time to concentrate on his own work. He was convinced that there were many talented people in universities who would do exceptional work if they were given the essential prerequisite, time—time free from routine duties of teaching, examination, administration, and committee work. Modern research required a lot of time to master new knowledge and techniques. This requirement of time should always be a consideration in the set-up of universities. He believed that the university was a place where major research should be conducted so that the research worker—a biochemist, for example—could get help and stimulus from mathematicians, physicists, chemists, engineers, biologists, and from philosophers and historians. Turning to the other feature of the present occasion, Professor Krebs said he was gratified to know that the Hebrew University was doing much to promote fundamental research, though one heard critical comments on the usefulness of this in a poor country like Israel where so many practical problems wanted attention. After Dr. A. Lerner had appealed for financial support for the Hebrew University of Jerusalem, Dr. Leonard Simpson proposed the health of the chairman, and Sir Henry Cohen briefly replied.

Cost of In-patient Treatment.—The hospital costing returns for the year ended March 31, 1953, were published last week by the Ministry of Health. Expenses have continued to rise, though there is a good deal of variation between the costs in the different regions. The table below shows the average cost of maintaining a patient for a week in various types of hospital, the figures for 1951–2 being given for comparison.

Type of Hospital	Average Weekly Cost per In-patient	
	1952–3	1951–2
Teaching hospitals, London	£24 18 8	£23 13 8
" " Provinces ..	18 13 9	17 15 8
General hospitals, under 50 beds ..	13 13 5	12 14 9
" " 51–100 " ..	15 7 5	14 7 2
" " 101–300 " ..	15 10 6	14 13 3
" " 301–900 " ..	15 12 1	14 11 7
Maternity hospitals	17 13 1	16 19 2
Tuberculosis "	9 19 5	9 6 7
Mental "	4 8 6	4 1 1

The Building for the Job.—The Nuffield Foundation has established a Division for Architectural Studies as part of its headquarters organization. This follows the success of the research team appointed in 1948 by the Nuffield Provincial Hospitals Trust to investigate the functions and design of hospitals. This team completed its work last year and its final report is expected shortly. The new Division is under the direction of Mr. Richard Llewelyn Davies, A.R.I.B.A., who led the former research team, and besides architects the staff includes a doctor, a nurse, a historian, and a statistician. The Division will work closely with the D.S.I.R.'s Building Research Station. Its first assignments are the problem of the care of children in hospital and the design of research laboratories.

Chloramphenicol.—The first British reports of fatal aplastic anaemia in patients who had been treated with chloramphenicol were published in the *British Medical Journal* 18 months ago.[1 2] Since then there have been many other references in medical journals to the toxicity of the drug. The risk of blood dyscrasia following chloramphenicol treatment cannot be accurately assessed from the figures available, but the Council on Pharmacy and Chemistry of the American Medical Association has recently published a statement[3] advising restriction of the use of chloramphenicol "to the treatment of typhoid fever and other serious infectious diseases caused by organisms controlled by chloramphenicol but resistant to other antibiotics or other forms of treatment." The Ministry of Health has also just issued a memorandum on this subject. After stating that it is impossible to determine the frequency with which blood dyscrasia follows chloramphenicol treatment since the total population at risk is not known, the memorandum concludes: "It is apparent that the incidence is low, since the condition is usually fatal and cases would therefore come to notice. When excessive dosage is avoided, the incidence must be very low indeed; thus no cases have arisen during the Medical Research Council's controlled therapeutic trials in pneumonia, whooping-cough, and infantile gastroenteritis. It cannot be too strongly emphasized, however, that the use of chloramphenicol is not without risk, and prolonged or repeated administration (especially of large doses) should be avoided, particularly in conditions such as chronic respiratory and urinary tract infections."

[1] Hawkins, L. A., and Lederer, H. (1952). *British Medical Journal*, 2, 423.
[2] Wolman, B. (1952). Ibid., 2, 426.
[3] *J. Amer. med. Ass.*, 1954, 154, 144.

American Surgeons in London.—A Section Meeting of the American College of Surgeons will be held at the Royal College of Surgeons, Lincoln's Inn Fields, from May 17 to 19. The programme includes symposia on gynaecology, cancer, and cardiovascular surgery, panel discussions on pre- and post-operative care, massive gastro-intestinal tract haemorrhage, and hand surgery, and operating sessions in London teaching hospitals. Further details will be available later.

Travelling Fellowships in Ophthalmology and Otology.—The Medical Research Council invites applications for travelling fellowships in ophthalmology and otology for the academic year 1954–5, for which special provision has been made by the Alexander Pigott Wernher Memorial Trustees. These fellowships are intended for suitably qualified medical graduates who are likely to profit by a period of work in ophthalmology or otology at a centre abroad before taking up positions for higher teaching and research in these branches of medical science. Candidates will be required to submit an outline of their proposals for work at a selected centre. The awards will normally be tenable for one year: no provision can be made for travelling grants for short-term visits abroad. The fellowships provide for the payment of a maintenance allowance at the rate of £650 per annum for a single Fellow or £900 per annum for a married Fellow, subject to appropriate adjustment in the case of fellowships tenable at centres outside the sterling area; in addition, an allowance is made for travelling and other approved expenses. Forms of application may be obtained from the secretary, Medical Research Council, 38, Old Queen Street, London, S.W.1, with whom applications must be lodged by March 31.

Grants and Fellowships for Research on Leukaemia.—The trustees of the Lady Tata Memorial Fund invite applications for grants, scholarships, or fellowships for research on diseases of the blood, with special reference to leukaemia, in the academic year 1954–5. Candidates with programmes of research on any aspect of malignant disease which may throw incidental light on the related problem of leukaemia will be eligible for consideration. Grants of variable amount are made for research expenses or to provide scientific or technical assistants for senior workers. Scholarships are awarded for the personal remuneration of workers carrying out approved research under suitable direction; their normal value will be £600 per annum for whole-time research, with proportional adjustment for work on a part-time basis. In addition, the trustees may award one or more Lady Tata Memorial Research Fellowships to workers with considerable research experience; the stipends of these fellowships will be at the rate of £1,000 per annum. All these awards are open to investigators of any nationality, working in any country in which it will be possible to make payments in the coming academic year. Further particulars and forms of application may be obtained from the Secretary of the (European) Scientific Advisory Committee, Lady Tata Memorial Trust, c/o Medical Research Council, 38, Old Queen Street, London, S.W.1. Applications must be submitted before March 31, and the awards will be announced by the trustees in June.

Research Studentships at Cambridge.—Details of the Elmore Medical Research Studentships are given at page 45 of our advertisement columns. They are open to graduates born anywhere in the Commonwealth (except Scotland) who wish to work in the Department of Medicine at Cambridge, under the direction of the Regius Professor of Physic. The studentships carry a salary of between £400 and £850 a year, and preference will be given to those interested in haematology.

Family Doctor.—The February issue, which is now available, contains medical articles on influenza, twins, coronary thrombosis, and phenobarbitone. Dr. Walter C. Alvarez, professor of medicine at the Mayo Clinic, completes his three-part series "How to Live with Your Nerves." Next month he will be writing on "How to Live with Your Blood Pressure." Evelyn Ford describes a valuable social service in "Invalid Kitchens," and Nicholas Ward, adapting the old nursery jingle, takes "This Little Pig Had Penicillin" as the title for an article on the use of antibiotics for fattening livestock. Fish lens protein, a substance alleged to be a medical cure of cataract and which has received considerable publicity in the lay press, is the subject of unfavourable editorial comment. *Family Doctor* costs 1s. 6d. and can be obtained through any bookseller.

Ministry of Health Art Club Exhibition.—Mr. Iain Macleod opened the annual exhibition of his Ministry's art club and the Hygeia Camera Club on February 1. An interesting feature was the showing of 12 pictures presented by individual members of the club to various hospitals.

COMING EVENTS

Study Circle on Medical Statistics.—A meeting will be held at the Westminster Medical School, Horseferry Road, London, S.W.1, on February 23 at 6 p.m. The subject will be "Medical Statistics in the Services."

Pan-American Congress of Otolaryngology and Bronchoesophagology.—The fourth congress will be held in Mexico City from February 28 to March 4. It is understood that the organizing committee would welcome representatives of British professional bodies.

Seventh Laboratory Animals Bureau Congress.—The congress will be held at Sheffield University on April 5 and 6. Applications for admission, which is normally limited to animal and laboratory technicians, should be made without delay to the Laboratory Animals Bureau, M.R.C. Laboratories, Holly Hill, London, N.W.3.

NEW ISSUES

British Journal of Venereal Diseases.—The next issue (Vol. 29, No. 4) is now available. The contents include:

SURGICAL ASPECTS OF TABES DORSALIS. Robert Lees.
FAMILIAL INVESTIGATION IN SYPHILIS. W. V. Macfarlane.
THE CONTEMPORARY DEFAULTER IN A V.D. CLINIC—FURTHER OBSERVATIONS. Gordon O Horne.
TRICHOMONAS VAGINALIS INFECTIONS IN THE MALE. F. Lanceley.
THERAPY OF LYMPHOGRANULOMA INGUINALE WITH 7218. C. D. Alergant.
RECTAL GONORRHOEA IN WOMEN. Tage Jensen.
RESEARCHES IN NON-SPECIFIC URETHRITIS. II. TREATMENT. R. R. Willcox.
UNITARY *v.* PLURAL CONCEPTION OF ANTILIPID ANTIBODY IN SYPHILITIC SERUM. Amal Kumar Mitra, Sunil Kumar Biswas, Sukumar Sen, and Narayan Chandra Bhattacharjee.
COMPLEMENT-FIXATION TEST FOR LYMPHOGRANULOMA VENEREUM IN NON-SPECIFIC URETHRITIS. A. D. Macrae and R. R. Willcox.
STABILITY OF THE ANTIGEN USED IN THE PRICE PRECIPITATION REACTION UNDER DIFFERING TEMPERATURE CONDITIONS. L. R. S. Macfarlane, C. K. Henderson, and F C. Pinion.
V.D.R.L. TUBE TEST. Aida Y. Djanian.
ANNOTATON: RECENT PROGRESS WITH THE TREPONEMAL IMMOBILIZATION TEST.

Issued quarterly; annual subscription £2 2s.; single copy 12s. 6d.; obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

Abstracts of World Medicine.—The February issue (Vol. 15, No. 2), which is now available, contains abstracts of important papers drawn from medical and other scientific journals published in some 20 different countries and in all five continents. The subjects covered range over the whole field of clinical medicine and include pathology, bacteriology, pharmacology, and chemotherapy; there are also sections dealing with public health, industrial medicine and toxicology, anaesthetics, radiology, and the history of medicine.

Issued monthly; annual subscription £4 4s., single copy 8s. 6d.; a specimen will be sent free on request.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Applications should be made first to the institution concerned.

Monday, February 8

INSTITUTE OF PSYCHIATRY.—5.30 p.m., lecture-demonstration by Dr. E. Stengel.
LONDON UNIVERSITY.—At Physiology Theatre, University College, 5.30 p.m., special university lecture in biochemistry by Professor C. Fromageot (Paris): Metabolism of Sulphur Amino Acids and the Cycle of Sulphur in Nature.
MEDICAL SOCIETY OF LONDON.—8.30 p.m., Meeting of Fellows. Discussion to be introduced by Mr. L. N. Pyrah and Dr. C. Enrique Dent: Recurrent Urinary Stone.

Tuesday, February 9

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. J. V. Dacie: Congenital Haemolytic Anaemia.
CHELSEA CLINICAL SOCIETY.—At South Kensington Hotel, a discussion on General Practice, to be opened by Dr. John Hunt, Dr. A. Talbot Rogers, and Dr. E. P. Scott.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. H. J. Wallace: Ano-genital Pruritus.
MANCHESTER MEDICAL SOCIETY: SECTION OF SURGERY.—At Medical School, Manchester University, 5 p.m., Mr. H. A. Haxton: Physics in Surgery.
ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., Milroy Lecture by Dr. D. Long: Pathogenesis of Rheumatic Fever.
ST. MARY'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Mr. Donald B. Fraser: Ectopic Gestation.
UNIVERSITY COLLEGE LONDON: DEPARTMENT OF PHARMACOLOGY.—At Physiology Theatre, 5.30 p.m., public lecture by Professor F. Bergel, Ph.D., D.Sc.: Some Chemical Aspects of Abnormal Growth.

Wednesday, February 10

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. R. W. Riddell: Practical Aspects of *Trichophyton rubrum* Infections.
INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Mr. H. P. Winsbury-White: Frequency and Other Disturbances of Micturition.
● LONDON UNIVERSITY: DEPARTMENT OF EXTRA-MURAL STUDIES and ATOMIC SCIENTISTS' ASSOCIATION.—At Beveridge Hall, Senate House, 7 p.m., Dr. J. F. Loutit: Radiation Hazards of Atomic Energy.
MANCHESTER MEDICAL SOCIETY: SECTION OF PATHOLOGY.—At Medical School, Manchester University, 4.30 p.m., Dr. T. H. Blench: The Law Looks at Medicine.
ROYAL FACULTY OF PHYSICIANS AND SURGEONS OF GLASGOW.—5 p.m., Finlayson Memorial Lecture by Professor Alan Moncrieff: Marasmus.
ST. MARY'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Dr. R. A. J. Asher: Lecture-demonstration in psychiatry.

Thursday, February 11

ALFRED ADLER MEDICAL SOCIETY.—At 11, Chandos Street, W., 8 p.m., Mr J. E M. Ayoub: Mental Reactions to Visual Abnormalities.
BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Professor H. B. Maitland: Anti-virus Immunity.
GLASGOW UNIVERSITY MEDICO-CHIRURGICAL SOCIETY.—At Glasgow University Union, 7.30 p.m., Mr R B Wright: Management of Thrombophlebitis of the Lower Limb and its Sequelae.
● HUNTERIAN SOCIETY.—At Savoy Hotel, London, W.C., annual dinner.
● INSTITUTE OF CHILD HEALTH.—5.30 p.m., Dr K. Soddy: The Invalid Chair.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr J. O Oliver: Blood and Bone Marrow in Skin Diseases (with colour film: Marrow Puncture).
INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5 p.m., Professor F. C. Ormerod: Malignant Disease of the Oesophagus.

LONDON UNIVERSITY.—(1) At Physiology Theatre, University College, 5.30 p.m., special university lecture in biochemistry by Professor C. Fromageot (Paris): Metabolism of Sulphur Amino Acids and the Cycle of Sulphur in Nature. (2) At Senate House, 5.30 p.m., special university lecture by Air Marshal Sir Harold Whittingham: Air Transport of Sick and Wounded.

NUFFIELD ORTHOPAEDIC CENTRE.—At Wingfield-Morris Orthopaedic Hospital, Headington, Oxford, 8.30 p.m., Dr. J. F. Brailsford: Manifestations and Complications of Paget's Disease.

OXFORD UNIVERSITY.—At Southfield School, Glanville Road, Cowley Road, Oxford, 8 p.m., Dr. A. G M. Weddell: Science and Medicine.

ROYAL ARMY MEDICAL COLLEGE.—5 p.m., Sir Harold P. Himsworth: Current Problems in Medical Research.

ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., Milroy Lecture by Dr. D. Long: Pathogenesis of Rheumatic Fever.

ST. ANDREWS UNIVERSITY.—At Physiology Department, Dundee, 5 p.m., Professor Alan Moncrieff: Marasmus.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., neurology demonstration by Dr. J. H. Paterson.

Friday, February 12

INSTITUTE OF DERMATOLOGY.—5.30 p.m., clinical demonstration by Dr. H. W. Barber.

LONDON UNIVERSITY.—At University College Hospital Medical School, 5 p.m., special university lecture in medicine by Professor A. M. Claye: Pain in Labour and its Relief.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Mr. D. Innes Williams: The Bladder in Congenital Spinal Cord Lesions.

ROYAL INSTITUTION.—9 p.m., Dr. C. Keith Simpson: Science in Crime Detection.

ROYAL MEDICAL SOCIETY, Edinburgh.—8 p.m., Professor R. A. Willis: Developmental Vestiges and their Pathology.

Saturday, February 13

ASSOCIATION OF CLINICAL BIOCHEMISTS (S.E. AND S.W. REGION) and ROYAL INSTITUTE OF CHEMISTRY (LONDON SECTION).—At Department of Zoology, the University, Reading, 2.30 p.m., physical methods in biochemistry. Papers and demonstrations.

SOUTH-EAST METROPOLITAN REGIONAL TUBERCULOSIS SOCIETY.—At London School of Hygiene and Tropical Medicine, 10.30 for 11 a.m., discussion between Mr. T. Holmes Sellors, Mr. F Ronald Edwards, and Dr J. G. Scadding: Place of Resection in the Treatment of Pulmonary Tuberculosis.

APPOINTMENTS

LIVERPOOL REGIONAL HOSPITAL BOARD.—B. M. Sedzimir, M.D., F.R.C.S.Ed., Consultant Neurosurgeon; N. O'Beirn, M.B., B.Ch., T.D.D., Assistant Chest Physician to St. Helen's area; G. V. Osborne, M.Ch.Orth., F.R.C.S Ed., Part-time Consultant Orthopaedic Surgeon to Southport Promenade Hospital; G. L. Shatwell, M.Ch.Orth., F R.C.S., Part-time Consultant Orthopaedic Surgeon to Ormskirk County Hospital and Rainhill Hospital.

MACARTHUR, PATRICK, M.D., F.R.F.P.S., D.C.H., Consultant Paediatrician to Scottish Northern Regional Hospital Board.

MANCHESTER REGIONAL HOSPITAL BOARD.—C. A. Borland, M.B., Ch.B., F.F.A. R.C.S., Consultant Anaesthetist, Lancaster and Kendal Hospitals; P. B. Kunkler, M.D., M R.C.P., D.M.R.T., and Dorothy Pearson, M.B., Ch.B., D.M.R.T., Assistant Radiotherapists, Christie Hospital and Holt Radium Institute; A. Clark, M.B., Ch.B., D.P.M., Assistant Psychiatrist, Whittingham Hospital; L. Parker, B.M., B.Ch., Consultant Pathologist, North Manchester Hospitals Group Laboratory; R. S. Savidge, M.D., M.R.C.P., Consultant Physician, Bury and Rossendale Hospitals; S. M. Laird, M.D., F.R.F.P.S., D.P H., Consultant Venereologist and Director of St. Luke's Clinic, Manchester, and the Venereal Diseases Clinics of Manchester Royal Infirmary, etc.; S. Falk, M.D., D.P.M., Consultant Psychiatrist to Bury and Rochdale Hospital Centres; G. M. Colson, B.M., B.Ch., M.R.C.P., Consultant Physician, Bolton and District Hospital Centre; S. G. McComb, M.D., M.R.C.P.I., Consultant Physician (Geriatrics), Bolton and District Hospitals; K. A. Rowley, M.B., Ch.B., F.F.R., D.M.R.D., Consultant Radiologist-in-charge, Blackpool and Fylde Hospitals.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Burn.—On January 1, 1954, at Guy's Hospital, London, S.E., to Peggy (formerly Bird), wife of Robert Burn, F.R.C.S., a son—Richard William.

Martin.—On January 20, 1954, at Bentley, Hants, to Audrey (formerly Dealler), M.B., B S. D.A., wife of Peter Martin, a brother for Gillian, Nicholas, and Robert.

Sudbury.—On January 31, 1954, at Swindon Maternity Hospital, Wilts, to Mary, wife of Squadron-Leader J. R. Sudbury, B.M., M.R.C.P., D.R.C.O.G., R.A.F., a son.

DEATHS

Elliott.—On January 6, 1954, in hospital, James May Elliott, M.B., B.Ch., Colonel, R.A.M.C., retired, of Highclere, Hutton Mount, Brentwood, Essex.

Elwin.—On January 8, 1954, at Ashtead, Surrey, George Richard Elwin, M.D.

Fraser.—On January 5, 1954, at the Royal Infirmary, Edinburgh, Thomas Lochhead Fraser, O.B.E., M.B., Ch.B., Colonel, late R.A.M.C., retired, of Elie, Fife.

Fuller.—On January 6, 1954, at his home, Kensington, London, W., Francis Frederick Fuller, M.B., Ch.B., formerly of Harley Street, London, W.

Hacker.—On January 4, 1954, at 28, Torrington Square, London, W.C., Henry Pollard Hacker, M.D., D.Sc., D.T.M.&H.

Hale.—On January 9, 1954, at Midhurst, Sussex, Robert Eugene Vaughan Hale, M.B., B Ch., late of Harpenden, Herts.

Jameson.—On January 3, 1954, at St. Leonards-on-Sea, Sussex, William Ernest Jameson, M.B., C.M., J.P.

Mackenzie.—On January 5, 1954, at 22, Queen's Gate, Glasgow, Alister Thomas Mackenzie, M.D., D.P.H.

Sutherland.—On January 9, 1954, at Edinburgh, Donald Sage Sutherland, T.D., M.D., of 2, Craiglockhart Terrace, Edinburgh, late of Manchester.

Thompson.—On January 6 1954, at Christchurch Hospital, Bournemouth, Arthur Thompson, M.R C.S., L.R C.P., of 997, Christchurch Road, Bournemouth, Hants, late of East Drive, Brighton, Sussex, aged 81.

Tomlinson.—On January 3, 1954, the result of a road accident, Dorothy Sylvia Tomlinson, M.B., B.S., of 20, Eastwood Gardens, Newcastle-upon-Tyne, aged 25.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Accidental Extra-venous Thiopentone

Q.—*What treatment is advised if thiopentone escapes outside a vein during an intravenous injection?*

A.—The treatment of accidental extra-venous injection of thiopentone is by no means decided. Injection into perivenous tissue is usually small in amount and generally requires little or no treatment. If there is much pain the application of heat gives some relief. An immediate infiltration of the area with a solution of 1% procaine with hyaluronidase might prevent tissue damage. In the case of inadvertent arterial injections, characterized by immediate severe pain in the hand and by the obvious flushing or blanching of the hand and forearm, an immediate intra-arterial injection, through the same needle, if possible, of, say, 10 ml. of 1% procaine is advocated, followed by a block of the stellate ganglion or brachial plexus on that side. In addition to this, the intra-arterial injection at the site of the original one of arterial dilators like papaverine and tolazoline is advised. Some have gone further and insist that heparinization of the patient should be started immediately, the operation postponed, and heparinization maintained for some days to avoid intra-arterial thrombosis. The limb should be carefully watched for the ensuing 24 hours, and any evidence of circulatory impairment or nerve involvement demands immediate consultation with surgical colleagues as to the advisability of exploring the brachial artery and the antecubital fossa. Prophylaxis against extra-venous injections, and particularly of the dire consequences of intra-arterial injection, lies in the use of dilute solutions of thiopentone—certainly never stronger than 5%—and in the use of veins other than those which overlie the bend of the elbow. Good veins are usually found near the radial side of the wrist, on the back of the hand, and on the outer side of the biceps muscle and tendon.

Exercises for Hernia

Q.—*A lay practitioner claims to be able to cure hernia by abdominal exercises. Has such a claim ever been submitted to controlled investigations, and if so what was the result?*

A.—Such a claim has not, so far as the writer knows, ever been submitted to controlled investigation. Bulging of the abdominal wall due to lax muscles can clearly be "cured" by exercises. Certain types of direct herniae, especially that variety sometimes spoken of as Malgaigne's bulgings, will respond to rehabilitation of this kind. An indirect hernia, unless very small, is unlikely to disappear with abdominal exercises alone; and, even if the swelling did go, the sac would still be present with the likelihood of later recurrence. It must be conceded, however, that the wearing of a truss by a young person with a small, narrow sac and a good internal ring, combined with the maintenance of good abdominal muscle tone, can result in apparent cure. The best-authenticated example of this is in the case of Sir Astley Cooper's inguinal hernia. This was first noticed in his late teens, and he wore a truss for about five years night and day. No further swelling was seen after this, and when Sir Astley died at the age of 72 a detailed post-mortem examination was conducted at Guy's Hospital by John Hilton. It is notable that a minute serous canal was found on the affected side. Umbilical, femoral, and incisional herniae will not be cured by abdominal exercises alone, but all sufferers from hernia benefit from maintaining the abdominal muscles in good condition.

Clotting Time in Coronary Occlusion

Q.—*Is there any change in the blood coagulability of patients suffering from coronary thrombosis? If so, has it prognostic value?*

A.—In patients suffering from acute myocardial infarction some workers have detected a change in the heparin-clotting-time, but there is no consistent change demonstrable in ordinary clotting time. Thus in one series[1] of 19 patients with acute myocardial infarction 14 showed rapid heparin-clotting-time (i.e., the blood samples were "resistant" to the action of heparin) compared with only one of 14 controls suffering from other heart diseases. On the other hand, other workers[2] have found no consistent change in the so-called heparin-tolerance test. On the whole I think it would be fair to say that no great value can be placed on the results of blood coagulation tests in prognosis which in the long run must depend on the state of the myocardium and of its blood supply, especially with regard to the likelihood of further damage, and on complications like thrombo-embolism.

REFERENCES

[1] Rosenthal, R. L., and Weaver, J. C. (1952). *Circulation*, **6**, 257.
[2] Hilton, J. H. B., Cameron, W. M., Mills, E. S., and Townsend, S. R. (1948). *Canad. med. Ass. J.*, **59**, 447.

Sympathetic Ophthalmia

Q.—*Under what conditions is sympathetic ophthalmia a possibility? Can it occur without a penetrating wound of either eye? What is the mechanism of its causation?*

A.—Perforating injury is the commonest cause of sympathetic ophthalmia, and this disaster is particularly to be feared when irritation is prolonged by incarceration of iris tissue or ciliary body in the wound. The next important cause is intraocular operation, especially cataract extraction and other procedures implicating the lens.

Sympathetic ophthalmia without any antecedent perforating injury or operation is exceedingly rare. Probably some of the recorded cases were not genuine, and in others there may well have been an inconspicuous and painless small wound of entry. I would not like to say that the condition is impossible without a perforation, but it probably does not occur.

The mechanism of causation is still not known for certain. Various organisms have been blamed. Some authorities believe that sympathetic ophthalmia is brought about by a virus conveyed by the optic nerve sheaths. Others regard the disease as an allergic outburst.

Treatment of Vitiligo

Q.—*What treatment is recommended for vitiligo? I have found autohaemotherapy helpful. Is this the general experience?*

A.—Although from time to time cases have been recorded in which vitiligo has healed following some form of local or systemic treatment, such cases are quite exceptional and it may even be doubted whether the treatment has really had any effect at all. The general consensus is, in fact, that no treatment is at all reliable. In recent years El Mofty[1] has recorded successful treatment by the internal and local use of "meladinine." This is a plant extract which has the property of sensitizing the skin; after it is applied the skin is exposed to ultra-violet light and the resulting erythema is followed by a return of normal pigmentation. El Mofty's patients have all been in Egypt; the treatment has also been used in France, apparently with success. Only in recent months have small supplies been available in the United Kingdom, and it is as yet too early to assess results.

In the absence of curative treatment a good deal can be accomplished by the skilful use of concealing creams. It is also sensible to protect the normal skin from sunlight so that it does not present such a contrast with the pale areas.

REFERENCE

[1] *Brit. J. Derm.*, 1952, **64**, 431.

Will the Eyes Change Colour?

Q.—*At what age can one assume that the colour of a baby's eyes will not change from blue to brown? Is it true that the colour change only goes in this direction, i.e., never from brown to blue; if so, why?*

A.—At no age can one safely assume that the colour of a baby's eyes will not change from blue to brown, except when both parents are of blue-eyed stock. However, if the change has not occurred by the age of 15 years, gross alteration in colour is unlikely, although I have seen a yellow margin appear in grey- and blue-eyed people after this age. Changes in the reverse direction, from brown to blue, occur only in pathological or senile conditions.

There is some evidence to suggest that little spots or masses of pigment may appear in the later decades of life, and that this tendency towards darkening of the iris is more marked in women than in men.

Renal Glycosuria and Hypoglycaemic Attacks

Q.—*Does renal glycosuria ever account for hypoglycaemic attacks?*

A.—It is doubtful whether renal glycosuria is ever the cause of true hypoglycaemic attacks. However, it is possible that in those cases in which there is a heavy loss of sugar associated with a very low threshold and an inadequate intake of carbohydrate a mild degree of hypoglycaemia may occur and possibly give rise to a sensation of weakness, etc. Even this must be very uncommon.

Cyanosis after Tattooing

Q.—*Is a transitory (24 hours) but very obvious cyanosis a recognized complication of tattooing? If so, what is the explanation? I have seen this in a healthy boy of 17.*

A.—Tattooing is performed by introducing colouring matter into fine punctures of the skin. The pigments most generally used are indigo, vermilion, and cinnabar. Indigo is an organic compound, while both vermilion and cinnabar are essentially sulphide of mercury, vermilion being the purest form. None of these materials is likely to cause transient cyanosis. The nature of the cyanosis is not stated, but it is reasonable to assume that it was due to methaemoglobin formation. In place of the usual pigments, it is possible that a tattooer might employ less inert colours, such as indian ink alone or combined with aniline black. In this connexion attention can be drawn to the report of an outbreak of cyanosis (methaemoglobinaemia) in newborn babies due to the use of unlaundered napkins marked with a marking ink of aniline black in aniline.[1] Cyanosis of this type is transient.

REFERENCE

[1] Howarth, B. E. (1951). *Lancet*, **1**, 934.

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